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# THE MEDICAL CLINICS OF NORTH AMERICA

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CLINIC OF DR C C BASS

TULANE UNIVERSITY

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## QUARTAN MALARIA

THE first case we have to present is one of quartan malaria, which shows some interesting features. I am able to present this case through the courtesy of Dr E Z Brown, who first brought it to my attention. The patient has been under observation for several days, during which time he has been under experimental treatment with stovarsol (acetylaminohydroxyphenylarsonic acid) for four days and under treatment with quinin during the past two days.

The patient is a white man, about sixty years of age. He gives his present address as Harvey, La., which is located on the Mississippi River only a few miles from New Orleans. He is a laborer working on barges running between New Orleans and Cincinnati. He has never been outside of the United States and has not worked or lived anywhere except up and down the river during the past four years. This is particularly interesting, in view of the diagnosis of quartan malaria that has been made, and of the further fact that this form of malaria is very rare in the United States and its transmission is limited to a very small region.

We get an occasional case of quartan malaria in persons coming from foreign countries. All the cases I have seen who were infected in this country gave histories which enabled one to trace their infection to the same region, viz., northeast Louisiana and southeast Arkansas. A few years ago I saw 2.

cases in Sunflower County, Miss, but both of these had been living just across the river in Arkansas and they were probably infected there. No doubt there are other regions of limited extent in which transmission takes place, but I have not happened to learn of them. It would be interesting to know why this form of malaria does not spread like the other two prevalent forms. It is quite likely that this patient may have been infected in the region referred to, since he would have been exposed during stops at towns and settlements along the river.

According to the patient's history, he had an attack of malaria, "regular chills and fever," he says, in 1892. He has not had it again until now, thirty-three years after the previous attack. This suggests the question of immunity from malaria. In regions where malaria prevails it is common to find persons who have lived in close contact with it for years, constantly exposed to infection, who have never had attacks of the disease. If we examine the blood of a number of such apparently immune persons, we find malaria parasites in some of them. They seem to have possessed sufficient immunity or resistance to the disease to prevent the development of clinical symptoms, although they became infected. Many of such persons finally throw off the infection without ever having clinical attacks. Others develop clinical symptoms as a result of the additional influence of conditions that tend to depress the resistance, such as childbirth, injury, surgical operations, digestive disturbances, etc. A good example is the case of the development of clinical attacks of malaria following eating large quantities of indigestible food. In malarious countries there is a common belief that eating heavily of such foods as green fruit, watermelons, muscadines, etc., is sure to bring on (malarial) chills and fever. Physicians who practice in regions where malaria is prevalent often see the development of active clinical malaria in previously healthy individuals following childbirth, severe injury, major surgical operations, etc.

There is abundant evidence that absolute immunity against malaria is very rare, if, indeed, it ever exists. During the past few years a great many experimental inoculations of malaria

have been carried out and there have also been a good many inoculations made for therapeutic purposes in the treatment of malaria. They all "take" when suitably inoculated except in a few very rare instances. One notable case is reported by Bunker and Kirby,<sup>1</sup> of the New York Psychiatric Institute. They inoculated 53 patients who had paresis one or more times with blood containing malaria parasites. All took except one striking exception who was inoculated four times with the same blood that took on the other cases, but he was never infected. This would look like a case of absolute immunity. There are a good many other cases in which the inoculation did not take the first time, but did take later. This would seem to indicate a variable degree of resistance to malarial infection in certain individuals.

One attack of malaria does not protect against subsequent infection, as is shown in our present case. It is interesting to note, however, that one or more attacks tend to protect against the more severe effect of subsequent attacks. This is especially true provided the first attack occurs during childhood. It has frequently been observed that when adults who have always lived in non-malarious regions go to malarious regions and get infected, the disease is very severe and not infrequently fatal. On the other hand, persons who have lived in the same region for a long time, who usually have had attacks of malaria or at least presumably have recovered from infection in childhood, have only the mildest forms of the disease. A very similar condition exists in pyroplasmiasis, or tick fever of cattle, which, by the way, resembles malaria in man in many ways. If cattle get infected when they are calves, they usually recover, but remain sufficiently resistant to the destructive effect of the disease afterward to enable them to withstand subsequent infections. On the other hand, cattle brought from regions where they did not get infected and therefore did not acquire this resistance when young will have the severest form of the disease and will usually die.

<sup>1</sup> Bunker, H. A., Jr., and Kirby, G. H., Treatment of General Paralysis by Inoculation with Malaria, Jour Amer Med Assoc, 1925, 84, 563

This patient was first seen seven days ago, at which time he stated that he had been having chills and fever more or less irregularly for a period of about three months. He took various remedies from time to time that different people told him about, including quinin, willow tea, "999," etc. He has had periods of temporary relief for a few days at a time, but the chills and fever kept coming back. He had been having them regularly during the previous two weeks, the last being on the day previous to his visit.

The significant findings on first examination were a slightly palpable spleen, temperature of 99.6° F, and quartan malaria plasmodia. The diagnosis was made upon the presence of characteristic quartan parasites. The most important characteristic of this species is the small number of segments, six to eight, in the mature schizonts or rosettes. These were found in all the blood specimens examined on the first and subsequent days until all parasites finally disappeared.

The case was considered a favorable one on which to try treatment with the new drug, stovarsol (acetylaminohydroxy-phenylarsonic acid). Favorable reports upon the use of this drug in malaria have appeared in the literature and we have received other unpublished favorable reports. With the patient's consent, he was put on one tablet, 0.25 gm, stovarsol t.i.d., and no other treatment. He was allowed and encouraged to stay up and about at his usual activities and to eat whatever he wished and to do anything he felt like doing. If we had taken him into a hospital and placed him on hospital diet and hospital regimen, we might have defeated our experiment. That is what has been done in most of the favorable cases reported thus far. When malaria patients are put to bed, given light diet, and a purgative, as is often the routine, the clinical symptoms usually become much lighter and they often stop entirely. In such cases one is likely to attribute to whatever treatment that may be given for the malaria effects that should not be attributed thereto.

Each day the patient returned for observation. His temperature at the time of these daily visits was 99.6°, 101.4°,

103.6°, 102.4° F There were fully as many plasmodia present each day as were found the first time There was therefore no improvement whatever in either the clinical symptoms or reduction in the number of parasites after four full days of treatment with stovarsol On the fifth day the stovarsol was stopped and the patient was put on the "standard treatment" with quinin At that time his temperature was 103.1° F, and many quartan plasmodia were present The next day, about twenty-four hours after the quinin was started, his temperature was 99.4° F, and only one parasite was found in quite a number of slides examined Today, not quite forty-eight hours after the quinin treatment was started, his temperature is 98.3° F and prolonged, thorough search of his blood fails to reveal any plasmodia

The results from the use of quinin in this case are not different from those obtained in practically all cases of malaria, regardless of clinical type or kind of plasmodia Clinical symptoms are controlled within forty-eight hours, often much earlier, in practically all cases, and always within seventy-two hours whenever quinin is given in sufficient doses I have no personal knowledge of any case in which clinical symptoms of fever or chills and fever due to malaria were not controlled within three days by as much as 30 grains of quinin daily

Sometimes plasmodia in small numbers may be found, especially in cases of estivo-autumnal infection, for several days Rarely the more resistant crescents may be found present for even a week or two in some cases, notwithstanding vigorous quinin treatment Gametes do not produce clinical symptoms and they die out in due time The very small numbers of other forms that may occasionally be found during the first days of quinin treatment are not sufficient to cause clinical symptoms It is believed that they usually represent individuals that have been swept out into the circulating blood only a short time before the specimen was collected and that they soon would have been killed

Malaria is one of the few diseases for which we possess a specific Quinin is a sure cure when used properly There is

the greatest difference of practice in the treatment of malaria with quinin. No method is more effective than what is known as the Standard Treatment, which was recommended by the National Malaria Committee in 1919 and first published in the U S Public Health Reports, vol 34, No 52, December 26, 1919, p 2959. It is as follows:

"For the acute attack 10 grains of quinin sulphate by mouth three times a day for a period of at least three or four days, to be followed by 10 grains every night before retiring for a period of eight weeks. For infected persons not having acute symptoms at the time, only the eight weeks' treatment is required.

"The proportionate doses for children are: Under one year,  $\frac{1}{2}$  grain, one year, 1 grain, two years, 2 grains, three and four years, 3 grains, five, six, and seven years, 4 grains, eight, nine, and ten years, 6 grains, eleven, twelve, thirteen, and fourteen years, 8 grains, fifteen years or older, 10 grains."

## PELLAGRA

Our next case is one of pellagra, which I am permitted to present through the kindness of Dr S C Jamison. The usual features of pellagra are now so well known that the disease no longer attracts special attention. The reason for presenting this case is that, in addition to the usual features, there are lesions distributed over the course of the large veins on the back of the forearms. I have never seen or at least have never had my attention called to lesions over the course of the veins nor have I ever seen it mentioned in the literature on this disease. These peculiarly distributed lesions in this case are especially interesting because they tend to shed further light upon the cause of the lesions in pellagra in general, or rather to confirm previously held views as to their cause.

The patient is a large negro man, about forty years of age, occupation, laborer in a saw-mill at Bayou LaFourche, La., where he has lived for the past several years. He came to the hospital about two weeks ago complaining of weakness, indigestion, and especially extensive lesions on the forearms and the backs of the hands. He stated that he has been sick for more than a month, but that previous to the onset of this present trouble he had not been sick in a number of years and that he had never had anything like the present illness.

When he was admitted, the lesions on his arms extended from the elbow in front down to the fingers. The backs of the forearms were not involved. Large patches of skin were loose. Beneath this was the weeping, inflamed deeper tissue. There was a large amount of seropurulent exudate present. This condition has rapidly improved under the influence of cleanliness and applications of zinc oxid ointment and also, no doubt of equal or greater importance, under the influence of time. The lesions are now dry, the loose skin has been removed except around the edges of the lesions where it is still peeling off and merges into the normal skin beyond. It will be noted that there is considerable dark pigmentation extending for an inch or more from the edge of the lesion from which the skin was lost. This pigmentation marks the extent of the milder erythema which was not sufficient to cause loss of the epidermis.

We find also a reddish-brown, triangular-shaped lesion about 2 inches across on the neck and over the upper end of the sternum. Two similar oblong lesions about 1 by 2 inches are noted on each side of the neck. These lesions are dry and will gradually exfoliate and finally disappear.



While looking at the lesions on the hands and arms, we noticed peculiar, dark, pigmented streaks running across the backs of the forearms. They are quite distinct and upon further investigation we find they are situated over the course of the large veins in this part of the arm. By constricting the arm and distending the veins, we note this quite striking pigmentation over the course of all the large veins in this part of the arm. Please note that this is the opposite side of the arm on which the typical pellagrous lesions are found and that apart from these pigmented streaks the skin appears



Fig 166—Pigmentation over the course of veins on the back of the arm opposite to the usual pellagrous lesion, the edges of which can be seen in the picture

normal. We note also that the appearance of these streaks is very similar to that of the skin at the edge of the other lesions on the arm except that it is actually darker (Fig 166).

Dark or black pigment is deposited in the pellagrous lesions in negroes and this is particularly noticeable in the lighter colored or mulatto negroes like this man. No doubt this circumstance and the particular exciting cause of these peculiar lesions in this case, which we will discuss presently, are responsible for their striking development which has attracted our attention.

Before attempting to explain these peculiar lesions over the veins, we wish to direct attention to some other lesions in this

case which are rarely observed, although they are often present. These are on the buttocks. They are about 3 inches in diameter. Exfoliation is still going on, but as the lesions shade off into the normal skin there is this reddish, very dark discoloration like that of the other lesions on his neck and hands and arms. These lesions are located over the points where the greatest pressure falls in sitting. It is true that there is more or less thickening and discoloration of the skin over these same points in normal individuals who sit a lot, but of course it does not approach the striking condition seen here.

Another thing to which attention should be directed in this case is the thickening and hardening of the skin over the nose, particularly the lower part both in front and on the sides. There are no lesions on the face in this case. Still this hard, thick, and very rough skin over the nose is present. The roughness seems to be due to forcing out, as it were, of material from the sebaceous glands, which is very hard. This hardened material sticks out as little points. It does seem to me that this condition occurs much more frequently and pronouncedly in pellagra in negroes than in whites. It is more pronounced, of course, in cases in which there are other pellagrous lesions also on the face, but it may be present, as in this case, without them. A similar condition is often noticeable over the chin.

Next we note that this patient's knee-jerks are greatly exaggerated. This condition is practically always present during the active stages of pellagra. It is so consistently present that it should always be looked for among the diagnostic signs. Of course it is not diagnostic in itself, but it is strongly confirmatory. It is interesting to note in this connection that in pellagra cases that grow worse and finally die, the exaggeration of the knee-jerks usually disappears. In fact, the response is below normal or entirely absent in most cases before death. I have been disposed to look upon the knee-jerks as a useful prognostic sign. As long as they are exaggerated the patient may recover. If they are subnormal or absent, recovery is highly improbable. I have never seen but one patient recover who had exaggerated knee-jerks and later great reduction.

We do not know the cause of pellagra. There are a number of more or less plausible theories, most if not all of which are, of course, wrong. There is no reasonable probability that there is more than one specific cause. Any other theoretic causes are therefore not true or at most are only contributing causes.

Although we do not know the specific cause of pellagra, we do know more about the exciting causes of the lesions and certain symptoms of the disease. The most notable lesions involve the skin and mucous membranes and the most noticeable symptoms involve the digestive system (tract) and the nervous system. You will note that the embryologic origin of all the tissues involved in these lesions and symptoms is the same, viz., epiblastic. In pellagra it seems that the epithelial tissues of the body, especially the skin and mucous membranes, have increased susceptibility to the damaging or irritating effect of various physical or chemical forces, or, to state it differently, the normal resistance or ability to withstand these forces is reduced or lost. This greatly lessened ability to withstand these influences, which would otherwise have no harmful effect, seems to be especially pronounced only during the acute or active stage of the disease and only during a comparatively short period. At this time, undue exposure to such things as direct sunlight, heat, x-rays, pressure or trauma, chemical irritants, etc., will cause the development of lesions on the skin. No doubt the duration and the degree of this susceptibility varies greatly with different individuals. Lesions caused by sunburn are situated on those parts that are particularly exposed at the time the damage occurred. On the arms they are usually on the upper side of the forearms. If the patient wore sleeves thoroughly protecting the arms, the lesions only develop as high as the cuffs and around the wrists. The backs of the hands and, when severe, the backs of the fingers are also involved. The palmar surfaces are not involved, both because they are tougher and because they are not exposed to the same extent.

Patients can often recall the time when the "sunburn" occurred as a result of special exposure at one or several times. One of the most striking illustrations of the effect of sunlight in

producing the skin lesions of pellagra occurred in the first case I ever had the opportunity of studying. This woman was suffering from digestive and mental disturbances and weakness, but had no noticeable lesions. Her physician advised her husband to take her for long buggy rides in the sun for the invigorating effect it was hoped this would have. She wore a large band ring on one finger, and when the quite severe lesions developed after a few days the part of the finger covered by the ring was perfectly clear, although the characteristic erythema running the usual course was present below and above this band, as well as on the backs of the hands and on the wrists. There are many illustrations of the effect of exposure to sun's rays in producing skin lesions in pellagra.

Pressure and trauma are also influences in producing certain of the lesions in pellagra. The best example of lesions produced in this way is the lesions occurring on the elbows in bedridden patients, never in others. If a patient becomes bedridden during the acute stage at which lesions may be produced, lesions, frequently quite severe, occur on the elbows caused by the pressure made by getting up in bed and resting on the elbows. Such lesions are almost always present in fulminating cases of the disease. I once saw an insane negro who, during the proper stage for producing lesions, spent a great deal of her time on her knees praying. She had very severe lesions on her knees.

This leads us to offer an explanation for the unusual lesions over the course of the veins on the backs of the arms in the case before us. The patient gives the history that at the time he developed the lesions on the front part of his arms and hands he was working in a lumber yard. His description of his particular work handling lumber indicates that he would have rubbed the backs of his arms a great deal against his clothes over his thighs and groins. With his veins greatly distended, as they would be during such work, it is easy to see that they would be subjected to much more friction than other parts. My opinion is that this explains these lesions.

Chemical irritants also cause the lesions in patients in the

susceptible stage Application of irritating ointments to the lesions and beyond usually increase the severity of the lesions and extend them beyond where they would otherwise develop I have seen lesions develop under the pendulous breast of a dirty fat woman, no doubt due to the irritation of acrid irritating perspiration which normally would have had no such effect

Irritation and damage of the mucous membranes of the digestive tract by chemical substances that are normally withstood, no doubt explains much if not all of the sore mouth, gastric symptoms, diarrhea, etc., that occur during active stages of the disease Vaginitis and moist lesions around the vulva and anus can be explained as being produced by irritating secretions that are normally ineffective

*There is no specific treatment for pellagra* Good hygienic conditions, nutritious food, and bland applications locally of such preparations as zinc oxid ointment, where needed, are advisable Irritating applications are harmful Most cases get well whatever is done Although quite a few patients die of pellagra, the number is very small as compared with the total number of people who have it If one must give some drug to satisfy his own desire to be giving something or the demand of the patient and the family to have some medicine, Fowler's solution of arsenic is recommended It probably does no good, but it is also probably harmless when given in proper therapeutic doses

## HOOKWORM DISEASE

OUR nextcase is one of hookworm disease of a rather severe type for this country. Hookworm infection is quite prevalent in many parts of the southern states, but this particular case illustrates certain special features of interest. The case also serves as a good illustration of the way in which the easiest disease to diagnose may be missed as a result of superficial examination. The patient is not present, but the history of the case will serve our present purpose.

While I was spending a few days of vacation during the past summer in south Mississippi, this patient was brought, by some relatives, to see me, with the hope that I could do something that would cure her Bright's disease, which had been diagnosed and for which she had already been treated by three different physicians in that locality. There was no question about the diagnosis in the minds of the patient or relatives or so far as they knew in the minds of the physicians who had treated her. In fact, the physician who had treated her last examined her urine and wrote a note to me stating that he had never seen so much albumin in urine.

The patient was a white woman, about thirty years of age, the wife of a poor farmer and laborer and the mother of 3 children, the baby now three years old. She has lived in Lamar County, Miss., all her life. She has never had any noteworthy illness until the present trouble came on. She was unable to name any definite time when it began. She stated that she had always been "puny" and that she thought she first noticed the edema ("dropsy") and weakness with marked dyspnea about a year ago. These were her chief complaints at the time I first saw her. Prior to that time she had been pale and "puny" for several years but never sick.

General anasarca and extreme anemia struck one at once. The feet and legs were more edematous than other parts, but the entire body, even the face, would pit more or less upon pressure. On the right leg over the tibia there was a large ulcer about 2 inches in diameter, with sharply defined edges and surrounded

by an inch or more of purple scar tissue which indicates that the ulcer had formerly been much larger. The patient stated that this ulcer was caused over two years ago by a scratch which got "dew poison" in it and this prevented healing. When the crude, filthy dressing was removed, there was a little bleeding followed by slow oozing of clear fluid from the ulcerated surface. This, of course, was the escape of fluid from the edematous tissue.

Another striking feature was the extreme pallor. All the tissues appeared almost bloodless. The conjunctiva and mucous membranes of the mouth were very pale.

Having no sphygmomanometer, I could not determine the blood-pressure, but judging by the feel of the pulse this was not high. The pulse rate was about 120 and fairly regular. Examination of the heart revealed considerable enlargement (dilatation) and to-and-fro murmurs over the precordium, loudest over the P M I. These gave the impression of, and no doubt were, the so-called hemic murmurs of extreme anemia due to great dilatation.

The laboratory equipment available consisted of a microscope and a mere handful of stains and reagents that had been taken along for use in studying some of the parasites of hogs and for such need as might arise in cases of the country people who frequently come as this one did, appealing for advice and help. The hemoglobin on the Tallqvist scale was about 15 per cent. Although it is well known that use of the Tallqvist scale is quite inaccurate especially on very low values, it is quite certain that the hemoglobin was very low.

I had no hemocytometer but could easily tell from the appearance of the stained smear that the number of cells was greatly reduced. In hookworm disease of such severe type as in this case there is great reduction of the total erythrocytes and still greater reduction of the hemoglobin, constituting anemia of the secondary type. It is not uncommon to find color-indices as low as 0.35 to 0.5. In this case one could not only recognize the reduction in the total number of cells by examining the stained smear, but he could see that the individual cells were poor in hemoglobin.

The differential leukocyte count revealed 24 per cent eosinophils, with a corresponding reduction in the other leukocytes. Here was further indication of hookworm disease. Although increased eosinophil counts may be found in other diseases and conditions, more or less increase is present in practically all cases of hookworm infection in which there are clinical symptoms. There is also increase in a great many cases in which there are not enough worms to cause other recognized symptoms. Hookworm infection should always be considered as one of the possibilities and it should be looked for when eosinophilia is found. This point serves to emphasize the value of the examination of the ordinary blood smear and particularly the differential count. Often eosinophilia is the first and only thing in a given case to suggest hookworm infection.

Upon inquiry as to attacks of ground-itch, the patient stated that she has had attacks of more or less severity from time to time as long back as she can remember and that about fifteen months ago she had a very severe attack. She could hardly walk for several days. No doubt she got an overwhelming infection at this time which was responsible for the unusually severe symptoms that were present. Most people living in those regions where hookworm disease prevails are more or less familiar with this condition. The microscopic larvæ in infested soil penetrate the skin of the feet, and sometimes other parts of the body, and set up an itching, burning, inflammatory process which runs a course of erythema, vesication, scabbing, and exfoliation over a period of about eight days. These larvæ finally reach the duodenum and jejunum, the normal habitat of hookworms, after passing through the heart and the lungs with the blood-stream. It takes about six to eight weeks from the date of an attack of ground-itch for the larvæ to reach the adult stage in the intestinal canal. This coincides fairly well with the onset of the more severe symptoms as related by this patient.

Examination of the urine revealed a very large amount of albumin. When acidulated and heated slowly in a tube over an alcohol lamp, there was so much coagulated albumin present that the tube could be inverted without the contents running out.



Although moderate or mild hookworm disease does not give rise to albuminuria, it is the rule to find it, usually in pronounced degree in severe cases such as this. No centrifuge was available but this is not necessary in making microscopic examination of urine, although desirable. Most of the casts and cells present in a urine will settle by gravity to the bottom of a tube in fifteen or twenty minutes. By pouring off the supernatant fluid and then draining the sediment on to a slide, one gets a fairly satisfactory specimen for examination. This was done and a few hyaline casts were found, but these were very few and there were no granular and epithelial casts such as one would expect to find in a severe case of nephritis. Generally in cases of severe hookworm disease in which even large amounts of albumin are present, there are few or no casts present, as was found to be the case in this instance. On the other hand, in true nephritis casts are always present. It developed later that the physician who examined the urine did not make a microscopic examination, but made his diagnosis on the presence of the large amount of albumin. This is another illustration of the importance of microscopic examination of urine and of the inadequacy of chemical examination in the diagnosis of nephritis.

A specimen of feces was obtained and examined microscopically. There were enormous numbers of hookworm ova present and an occasional ascaris egg was also found. From five to ten or more hookworm ova could be found in almost every low-power field in the ordinary preparation. It was not practical to make an egg count, but it would have been interesting in order to have been able to estimate more accurately the probable number of worms present. Basing my guess upon general impressions of this and of other specimens in which more accurate counts were made, I would think it likely that this patient had somewhere between 2000 and 5000 hookworms. No wonder she had extreme anemia and other severe symptoms, with so many blood-sucking parasites draining her blood daily for months and years. It is remarkable that she could have survived this drain as long as she had. She might not have survived it much longer.

Attention should be called to the fact that, although the anemia, general symptoms, urinary findings, blood examination, and history of ground-itch all suggest hookworm disease the definite diagnosis was made by finding ova in the feces. Without this we could not have made an absolute diagnosis. The only other way would have been by giving a suitable vermicide and finding the worms in the stools.

The patient was advised to take 1 c c oil of chenopodium at 6 A M 1 c c at 8 A M, and a purgative dose of magnesium sulphate at 10 A M. This treatment was to be repeated once a week. The patient was seen again after the third course. No hookworm or ascaris ova were found in the feces at this time. The patient looked and said she felt like a different person. She had lost 26 pounds (most of her edema). Although still quite anemic there appeared to be the greatest improvement in this regard. There was still a little edema in the feet and legs but none demonstrable elsewhere. The ulcer on the leg was about half the former size and appeared to be healing rapidly. The hemoglobin was estimated to be 35 per cent. Tallqvist. There was a faint trace of albumin in the urine.

Although this patient has not been seen again, a report received about two and a half months after she was first seen was to the effect that she had continued to improve and that she was then perfectly well. It is remarkable how rapidly such patients improve when they are relieved of their infection. No tonic or other treatment is needed to hasten convalescence and it is not likely that so-called tonic drugs of any kind would hasten it.



## AMEBIC DYSENTERY

My last case is one of amebic dysentery that was also seen in south Mississippi during our vacation. This patient will also have to be presented *in absentia*.

The patient, a very poor widow woman, about thirty-five years of age, came seeking help for "a bowel trouble" from which she had suffered for over two years. She could neither read nor write and her dress and appearance indicated extreme poverty and privations. Her distress and helplessness made a touching appeal to one's sympathy and whatever ability he might possess to help her. She stated that the present trouble began over two years ago, at which time she had an acute attack of dysentery with many bloody mucous stools and great tenesmus. This lasted for over three weeks, during which time she became very weak and emaciated. She lived in the "back woods" several miles from the nearest physician, and was unable to get him to come to see her because she could not pay him. He did send her some medicine based upon the best description of her case that her little boy could give him. The acute attack passed off, but she continued to have more or less pain and discomfort in the rectum and lower abdomen. Since that time she has had several acute attacks somewhat similar to the first one, followed by intervals during which she suffered much less and usually somewhat regained her strength. However, she has led a life of misery and great suffering for over two years. She is just now improving following a severe acute attack during which she had two very large intestinal hemorrhages which have further added to the weakening effect of acute dysentery.

The patient states that during the time she has been ill she has been under the treatment of two physicians, each for considerable periods of time. She would go to see them during remissions, and they sometimes sent medicine during the acute attacks. She does not know what treatment she received, but from the description I am certain it was not the specific treatment, ipecac or emetin, for amebic dysentery. Whether she was benefited by treatment seems doubtful. At any rate, she was still suffering as much as ever.

The most noteworthy condition noted upon inspection was emaciation. The patient probably weighed about 90 pounds, when she should weigh, for her build and height, about 140 pounds. One notes that the muscles of the arms and legs particularly are soft and flabby, a condition usually resulting from attacks of acute dysentery. This results largely from malnutrition. It is the experience of patients suffering from inflam-

matory and ulcerative diseases of the rectum and colon, as in this case, that taking food or even drinking water or other fluids causes and increases tenesmus. This is so much so that patients avoid taking food and water as much as they can. It is common for such patients to believe that such food or water promptly causes griping and usually a bowel movement. This usually consists of only a small amount of mucus or mucus and blood, and not of the food or drink which caused the passage. The explanation is that the act of deglutition causes waves of peristalsis to pass along the entire digestive tube, and when these reach the inflamed, ulcerated colon and rectum, griping pains are produced, accompanied by a feeling of necessity to evacuate. The same movements have no such effect upon the normal colon and rectum. This greatly increased pain and discomfort caused by the taking and the later digestion of food leads the patient to abstain from it as much as possible. There is also more or less feeling of nausea or anorexia accompanying the tenesmus and discomfort in the lower abdomen and in the rectum. The resulting reduction of the water intake results in more or less dehydration of the tissues in addition to the malnutrition from the lessened intake of food.

We are unable to make out any abnormality in the lungs or heart. The pulse rate while the patient was in the sitting position was 84 which may be considered low for a weak woman like this. A slow pulse is the tendency in dysentery of whatever origin. The spleen was not palpable, and especially careful examination of the liver indicated no enlargement but possibly slight reduction in size. The abdomen was flat, rather hollowed out, and there was considerable tenderness upon palpation along the colon, especially the descending and sigmoid colon. Palpation over this region caused tenesmus and a desire to evacuate. One could feel through the thin abdominal wall what, no doubt, was the thickened sigmoid.

No total blood-count could be made for lack of apparatus, but the hemoglobin on the Tallqvist scale was 80 per cent. This is quite high for a patient who has been suffering for so long a time from a weakening disease in which there is loss of

blood during the acute attack, and especially in the light of the history given by this patient of two recent large intestinal hemorrhages. What is the explanation? The deprivation of the tissues and the blood of water because of the greatly lessened intake has resulted in concentration of the blood. It is not uncommon to get total erythrocyte counts of 6,000,000 cells during attacks of acute dysentery. Even the leukocyte count is increased, and this should be allowed for in interpreting cell counts in such cases. The differential count is of more value in such cases as an indication of pyogenic or septic infection. The count in this case showed the percentages to be within normal limits.

A stool was obtained. It consisted of some bloody mucus. Some of the grayish particles found in this were fished out and put on a slide and covered with a cover-glass for microscopic examination. The diagnosis stood out in the first field under the microscope. There were many actively motile ameba, many of which contained erythrocytes. These were recognized as undoubtedly *Endameba histolytica*, the species that causes amebic dysentery in this country and in most warm regions of the world. Although the species of ameba was somewhat doubtful, it is certain that it was a pathogenic species. For all practical purposes we may consider ameba that phagocyte erythrocytes as pathogenic.

No proctoscope was available, but by digital examination one could feel that there was ulceration and thickening of the walls of the rectum as high as the finger could reach. No doubt the same condition extended much higher into the colon. One must see autopsy specimens from amebic dysentery to fully appreciate the character and extensiveness of these lesions. Such specimens serve to warn one against expecting unreasonable results from treatment. One realizes from such specimens that however perfect the specific treatment may be against the ameba, it must take a long time for such lesions to heal. Even then the tissues must be greatly weakened and impaired by the resulting scar tissue.

What was done for this patient was to give her a note to her former physician telling him what had been found, and sug-

gesting the usual line of specific treatment which can be expected to bring about rapid improvement and perhaps final recovery. She has not been heard from since, but from past experience we can predict that she has been relieved from her former distressful condition. Permanency of the results is not so certain, but persistence in proper treatment usually yields satisfactory results.

This case is given here because it presents certain interesting features and serves as a basis for discussion of some important points relative to the disease. One point of interest is that this woman had never lived or visited more than 40 miles from where she now lives and where she first developed the disease. She has lived in unhygienic surroundings and in more or less of a primitive way. The chances of infection were greater because of these conditions, but amebiasis is by no means limited to the lower, poorer classes. However, those of the better class who get it can usually trace their infection to living under primitive conditions with regard to drinking-water. Drinking-water contaminated with feces is the chief source of infection. Ameba carriers, some of whom may never have had recognized clinical symptoms, are frequently the source of contamination. Amebiasis and amebic dysentery may be encountered, as in this case, in the most remote parts of the country. It is endemic throughout most of the southern states.

This case brings out another point of interest, which is the fact that such a case in which the clinical symptoms pointed so definitely to the nature of the disease and in which the definite diagnosis could be made so easily by microscopic examination, could go so long without diagnosis and proper treatment. No microscopic examination had been made. The case emphasizes also the importance of the microscope as an aid to diagnosis. Regardless of the clear-cut clinical symptoms which pointed as strongly as possible to amebic dysentery, a definite diagnosis could not have been made except with the aid of the microscope. In this case it was of the greatest importance not only to diagnose dysentery, as the clinical symptoms and the physical examination only would permit, but to diagnose amebic dysentery. This is particularly true because we possess a specific remedy for this

form of dysentery which does not effect favorably dysentery due to other causes. The value of microscopic examination of stools in the diagnosis of amebic dysentery is comparable to the value of blood examination in malaria. In both diseases intelligent use of the specific remedy rests upon the diagnosis made with the microscope. Clinical symptoms, even when quite typical, are nothing like as reliable as the certain microscopic examination. One is not prepared to manage either of these diseases properly, as is also the case in many other diseases, without this facility.





# CLINIC OF DR GEORGE S BEL

## CHARITY HOSPITAL

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### PRIMARY CARCINOMA OF THE LUNG

THE patient before you this morning presents signs and symptoms illustrating some chronic intrathoracic pathology of a grave nature. The case is worthy of serious consideration because of the manifestations of distressing symptoms, and the opportunity it affords for accurate and intelligent interpretation of the signs and symptoms, aiding as they do in a discussion of the differential diagnosis and a determination of the underlying pathologic phenomena.

**Case History**—The patient has been under our observation about six weeks. He is fifty-eight years of age, married, a contractor by occupation. He complains of coughing and pain in the chest for about five months, with gradual loss of weight and resultant general weakness. The pain at first was dull in character, but later became intense, severe, and agonizing.

His family history is unimportant.

He has had the usual diseases of childhood, but denies having had rheumatism, gonorrhea, or syphilis. He states that he has always enjoyed good health.

Habits in regard to eating and sleeping are regular. Smokes moderately, but abstains from alcohol.

His present illness dates to about five months ago, when he began to cough. Coughing comes on in paroxysms, with hoarseness at times. Pain in left side of chest is fairly constant, necessitating strapping on one occasion. A general feeling of weakness is noted after coughing spells. This cough is of a distressing, harassing type accompanied by expectoration of a mucopurulent material, which material has become jelly-like in consistence, but with no offensive odor. There is pain, severe, stabbing, and cutting in type, and dyspnea is marked. At times the patient expectorates blood, as much as 4 ounces on one occasion.

**Physical Examination**—The first and subsequent physical examinations were made by Dr. Hobson and myself.

Physical examination shows a fairly well nourished man complaining of a paroxysmal cough which leaves him exhausted. There was no expectoration in the beginning. He has consulted throat specialists in an attempt to get relief.

The skin, head, eyes, nose, throat, and muscular and glandular systems are negative. Neck normal.

Heart not enlarged, normal sounds, no murmurs or thrills. Radial pulse regular, 80 beats to the minute, and of good volume. Blood-pressure—systolic 132, diastolic 80.

Superficial arteries somewhat sclerosed.

The spinal column and osseous system negative.

**Lungs**—*Inspection*—Slight limitation of movement of left side, later some distention of veins in left side of neck and left arm.

*Palpation*—Confirmed above findings, absence of tactile fremitus.

*Percussion*—Impaired resonance over lower left chest extending from fifth rib in anterior axillary line to about fourth rib in midscapular line and below to lower border of lung.

*Auscultation*—Impaired breath sounds, also whispered and spoken voice sounds over above area. Later bronchial breathing present, with bronchophony and whispered pectoriloquy.

Abdomen symmetric, no tenderness or rigidity elicited on palpation, liver negative. Spleen and kidneys not palpable, superficial and deep reflexes all normal. Rectal examination reveals no abnormalities, prostate soft, not tender or enlarged. Extremities and genitalia normal.

The blood examination shows

Red blood cells	4,000,000
White blood-cells	8,500
Hemoglobin	60 per cent
Differential count	
Small mononuclears	24 "
Large mononuclears	4 "
Neutrophils	71 "
Eosinophils	1 "
Basophils	0

Blood Wassermann reaction negative.

Urine shows trace of albumin and a few hyaline casts.

Stool. Examined on two occasions and found negative for parasites or ova. No occult blood.

**Roentgenogram** First report. Heart and aorta negative.

**Lungs** Left side area of consolidation, more or less central, corresponding to the eighth to tenth rib posteriorly and the fifth to seventh rib anteriorly, extending from the left border of the heart for a distance of 2 to 3 inches to the left.

Second report (four weeks later). Area of consolidation in the left lower lung about same size as last examination. The lesion is not as diffuse, being better delimited at its margins.

**Discussion**—As you note, the patient's present illness dates back five months, and, interesting to observe, he has been able to pursue his usual work until recently, when, on account of the obstinate and violent cough, the persistent and agonizing pain in the chest (which pain grew progressively worse and was only partially relieved by opiates), and the gradual loss of weight and muscular weakness he became completely incapacitated

**DR BEL** What is the duration of the present illness?

**STUDENT** Patient has complained of his chain of symptoms for the past five months

**DR BEL** It is evident from the history, symptoms, and signs that we are dealing with (1) a chronic disease, (2) the pathology is intrathoracic and seems to be of a grave nature Tell me the results of other laboratory tests that have been made

**STUDENT** Lumbar puncture—spinal fluid was negative  
Luetin test negative Gastric contents normal

**DR BEL** Was the sputum examined?

**STUDENT** Yes, several times, and always negative for acid-fast bacilli There was at first small amounts of mucopurulent sputum occasionally blood streaked, later the expectoration occurred at greater intervals but in larger amounts, containing material appearing to be broken-down lung tissue No examination of such material has as yet been made There is a secondary anemia

**DR BEL** Yes, the blood-picture is that of a secondary anemia What has been the temperature range?

**STUDENT** Varies from 97° to 100° F

**DR BEL** The fever is probably due to secondary infection resulting from breaking down or ulceration of the supposed tumor mass What interpretation do you make of the Roentgen-ray examinations?

**STUDENT** Roentgen-ray examination shows an area of consolidation in the left chest

**DR BEL** Was a gastro-intestinal roentgenologic examination made?

**STUDENT** Yes, the roentgenogram of the gastro-intestinal tract was negative

DR. BEL: Was a rectal examination made?

STUDENT: Yes, on two occasions careful digital and proctoscopic examinations of the rectum were made, and revealed no abnormalities.

DR. BEL: Let us now summarize the salient points of this case. We have a man fifty-eight years old whose illness began about five months ago with cough and pain in the chest, the cough and pain at first were moderate in type and gradually grew more frequent and intense. At first there was only scant sputum, later followed by mucopurulent and bloody sputum in large quantities but at no time was the sputum or breath offensive. The paroxysms of coughing were associated with much pain and dyspnea. There has been progressive loss of weight and strength.

Physical examination reveals a middle-aged man who, apparently, has lost considerable weight. The chest examination shows evidences of a mass in lower part of left lung, this being confirmed roentgenologically.

All laboratory tests negative except for a secondary anemia.

We have now to consider the various pathologic possibilities. What are they?

STUDENT: Pulmonary tuberculosis, aneurysm, pulmonary abscess, syphilis of lungs, and pulmonary neoplasm.

DR. BEL: Yes, I believe that that covers the possibilities quite well. Let us now consider pulmonary tuberculosis. As there are no physical evidences at the apices of the lungs and as no acid-fast bacilli were found in the sputum upon repeated examination, I feel that we can disregard tuberculous infection in the case.

Next let us consider lues. Negative history, negative blood Wassermann, negative cerebrospinal fluid, negative luetin test, and finally non-improvement upon antisyphilitic treatment, which you told me was administered, eliminates the possibility of a syphilitic lung.

Aortic aneurysm must be considered as a possibility. Here, again, negative history, negative Wassermann and luetin tests, the absence of auscultatory and other aneurysmal signs, rapid

loss of weight and strength, and the lack of improvement and relief of pain when placed absolutely at rest in bed, together with the r-ray findings, all rule out aortic aneurysm

Pulmonary abscess may be differentiated by the absence of previous infection elsewhere, especially lobar or bronchopneumonia, inhalations following throat and nose operations, particularly tonsillectomy, and finally, the absence of such symptoms of sepsis as fever, chill, sweating, leukocytosis. Again, the sputum is usually very offensive in an abscess of lung

After taking into consideration the above differential diagnostic facts and the history of the case, its symptoms, signs, laboratory findings, and progress, I must conclude that we are dealing with a malignant pulmonary new growth. However, as the inevitable finale will soon accrue, postmortem findings will determine the exact nature of the morbid process. If this is a neoplastic lung condition let us briefly review the pathologic possibilities

The lungs are, comparatively speaking, rarely the seat of tumors. However, a variety of both primary and secondary growths occur

Sarcoma is the most frequent connective-tissue tumor of the lungs. Such tumors may originate in the lymphatic glands surrounding the bronchi at the roots of the lung, or those surrounding the smaller tubes within the lung proper, from the lymphatic vessels themselves, or from the subpleural or other connective tissue of the lung itself. Primary sarcoma is much rarer than secondary

Of the epithelial tumors carcinoma is the only form to be considered, although adenomata of the lungs have been described. Carcinomatous tumors may start from the mucous glands of the larger bronchi or from the epithelium of the small bronchi. Sometimes squamous-celled carcinoma may originate in the epithelium of the terminal bronchioles and alveoli

DR BEL What is the prognosis if such a diagnosis be correct?

STUDENT Exceedingly grave, usually fatal

DR BEL Yes, death invariably results after a period of several months, usual duration being from six to ten months. Now, as to the treatment, what can we do to help this patient?

STUDENT There is no successful treatment for malignant disease of the lung. Surgical treatment is not advocated. Radium and deep therapy may be of some benefit.

DR BEL Yes, radium and deep therapy have been known to produce some improvement and offer a little encouragement, it, therefore, is to be recommended. The more distressing symptoms—cough, dyspnea, and pain—must be relieved by sedatives.

**Subsequent History of the Case**—Radium and Roentgen-ray treatment were employed, but the patient grew progressively worse and began to expectorate a large quantity of purulent material, frequently bloody in character, but at no time offensive.

About this time the anxious relatives, looking in all directions for assistance, called in a surgeon, who very promptly disagreed with our diagnosis of pulmonary malignancy, and insisted that the patient was suffering from a large pulmonary abscess, and recommended immediate surgical intervention. He performed a thoracotomy under local anesthesia, about 2 inches of the eighth rib being resected. The pleural cavity was found walled off at this point and an accumulation of about 1 pint of seropurulent fluid found. The finger was then passed into what was apparently an abscess cavity. It was not thought advisable to explore further or examine the parts with any great detail at the time due to the patient's condition. The patient died a few days after the operation and from the necropsy report the following salient points are noted:

**Anatomic Diagnosis**—Primary carcinoma of the lung (left more marked). Secondary carcinoma of the left kidney, parietal pleura, and peribronchial lymph-nodes.

Atelectasis of the left lung.

Thoracotomy wound of the left thoracic wall at the level of the eighth rib.

**Microscopic Diagnosis**—Gland-cell carcinoma of the left lung suggestive of bronchial origin. Pneumonia and pleurisy of the left lung.

*Lymph-nodes* —Secondary carcinoma

*Prostate* —Hypertrophy

*Kidney* —Secondary carcinoma, cloudy swelling, infarction (tumor cells)

*Liver* —Intralobular degeneration with foci of suppuration and pigmentation

*Spleen* —Passive congestion, pigmentation, and slight fibrosis.





# CLINIC OF DR JOHN H MUSSER

## CHARITY HOSPITAL

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### CLINICAL MANIFESTATIONS OF SPRUE AND RELATION OF THE DISEASE TO PERNICIOUS ANEMIA

SPRUE is a disease which up until the past few years has been considered purely a disorder of the Tropics. Cases had been recognized from time to time in the United States but these patients had all given a history of residence in the Tropics of prolonged duration. In fact, the first case in New Orleans, which was described by S. K. Simon<sup>1</sup> in 1911, occurred in a patient who had lived for seventeen years in Nicaragua. Within the past ten years, however, physicians in the southern states have been discovering cases originating in this section of the country, and occasional cases have been reported from European countries (Italy). In the east, according to Manson-Bahr,<sup>2</sup> the disease extends as far north as the 50th degree of latitude, well above the northern boundary of the United States, and as far below the Equator as the 25th degree of latitude. It may be seen from this very brief review of the geographic distribution of sprue that it can hardly be called a tropical disease, in the sense that it is endogenous to the Tropics, and that the usual qualifying adjective, "tropical," employed when writing of the disease, should be omitted. As the disease occasionally arises spontaneously in warm temperate climates, and as knowledge of the manifestations of the disease spreads more and more frequently will cases be recognized. Furthermore, as intercourse with and residency in Central America is

<sup>1</sup> Southern Med Jour, 1911, 4: 466

<sup>2</sup> Practice of Medicine in the Tropics, Blam & Archibald, Oxford Medical Publications, 1923, vol. III, p. 2249

increasing, patients will present themselves for treatment who have returned to this country after a more or less prolonged stay in the Tropics. It behooves you, therefore, to be able to recognize a case of sprue and to know something of this disease, which is not a rare disease occasionally imported from tropical or subtropical countries, but which will be found to be more and more prevalent in the States as time goes by.

**Case Report**—The patient I wish to present to you today is a native of New Orleans, who has never been out of this country. He is lieutenant in the city fire department and was born in 1882. He gave the following history on admission to the Charity Hospital, January 3, 1925.

**Present Illness**—This began in June, 1924, with diarrhea, when the patient had from two to three to ten to twelve stools in the twenty-four hours. He had no appetite and began to lose weight. At the same time a sore mouth developed, with soreness of the inside of the lips, the roof of the mouth, and the tongue. His mouth became watery and he was often extensively salivated at night while asleep. The diarrhea and the stomatitis have always been present at the same time. Sometimes there are intermissions of two or three days and then the intestinal disturbance recurs. This condition has kept up since last June and with it there has been a rather marked loss of weight, the patient having lost 60 pounds since that time. He complains also of marked weakness, which has become so pronounced that he is now unable to work. After eating there is considerable gas and belching and at times he is much nauseated and vomits. His sleep is much disturbed by distention of the abdomen and a feeling of discomfort associated with it. He has a slight cough, but no disturbance of the cardiac or renal systems. The family history and the past history are uneventful. He has always enjoyed good health since the time of childhood and has had no serious operations or injuries. A hemorrhoidectomy was performed a year ago. He has been free from venereal infection and has several children. He has been connected with the fire department for some years.

**Physical Examination**—At the time of his admission notes reveal nothing of moment except that he was well developed but poorly nourished and appeared very anemic. The mucous membranes of the mouth were very anemic. No note was made of his tongue. The heart and lungs showed nothing of importance and the abdominal examination is recorded normal in every respect.

**Subsequent History**—Patient was in the hospital for a period of approximately a month. During this time the notes show that he was complaining chiefly of a sore tongue and diarrhea the first two weeks while there. Within a period of about three weeks, on a light diet and acidophilus milk, his condition had improved materially and he was soon up and around the ward. Several times he had a slight return of the diarrhea and of the sore tongue.

Laboratory examinations were as follows. *Gastric contents* after Ewald meal, free hydrochloric acid 15, total acidity 52. *Stool examination* showed

CHART SHOWING BLOOD-COUNTS OF PATIENT WITH SPRUE

Date.	Hemo- globin.	Red blood- cells.	Color- index	White blood- cells	Remarks.
1/ 5/25	50	1,850,000	1 4+	2750	Polys, 46 per cent Small mono, 50 per cent Marked anisocytosis Marked poik- ilocytosis
1/ 8/25	45	1,460,000	1 6+		
1/12/25	55	2,440,000	1 1+		
1/15/25					Fragility Hemolysis begins 0 42 Complete hemolysis, 0 28
1/26/25	60	2,220,000	1 3+		
2/10/25	60	2,675,000	1 13+	3500	Weight, 174 pounds Polys, 72 per cent S M, 24 per cent
3/ 2/25		3,875,000		5500	Poyls, 62 per cent S M, 30 per cent
3/16/25	73	3,865,000	1 1+		Polys, 64 per cent S M, 25 per cent
3/30/25	75	3,580,000	1 1+	3800	Polys, 72 per cent S M, 21 per cent
4/20/25	75	4,075,000	0 9+	5750	Polys, 63 per cent S M, 26 per cent
4/26/25	75	4,740,000	0 7+	7500	Polys, 61 per cent S M, 23 per cent
5/11/25	75	4,790,000	0 7+	5250	Polys, 70 per cent S M, 19 per cent Weight, 187 pounds
5/25/25	70	3,805,000	0 9+	5000	Polys, 62 per cent S M, 30 per cent—after sharp re- currence
9/30/25	80	3 415,000	1 1+	4750	Polys, 74 per cent S M, 23 per cent L M, 3 per cent

liquid stool with active carbohydrate fermentation, no mucus, pus, or blood, fats and fatty acids in abundance, numerous *Trichomonas intestinalis*. Urinary examinations were normal, urobilin was not present. Gastrointestinal Roentgen ray was negative, as was the Wassermann. The Roentgen ray of the teeth showed advanced pyorrhea. The composite chart on page 897 shows his blood counts while in the hospital and since he has been under observation in the medical clinic. I had several examinations of the feces made for monilia while he was in the ward, but these fungi were never found at that time.

Lieutenant D. has been coming regularly to the dispensary up to the present time. He has been gradually increasing his weight so that he now weighs approximately what he did before he was taken sick. I have kept him on the acidophilus milk and given him injections of sodium cacodylate. He has been reporting once a week up until the present time. From time to time he has attacks of diarrhea lasting twenty-four hours and it is interesting to note that this is usually preceded by a marked soreness of the tongue, the burning and discomfort being so great that he cannot take cold drinks, hot food, and so on. May 11th the patient was seen by Dr. Castellani, who thinks that undoubtedly the symptoms and other findings are those of a case of sprue.

Repeated examinations have been made from scrapings of the tongue in order to determine if *Monilia psilosis* was present. The latter part of May Dr. Butler again cultured the stools and was able to get out a pure culture of a yeast which fulfils all of the cultural and morphologic characteristics of the *Monilia psilosis* as outlined by Castellani and by Ashford.

The patient, as you see him today, is a well-nourished, healthy looking man. You see on the tip of his tongue an area on which there is some denudation of epithelium. It is surrounded by rather prominent red fungiform papillae, while the whole tongue is markedly fissured. His examination otherwise shows him to be a strong, husky appearing male in whom there are no discoverable physical abnormalities or pathology.

**Stool Frequency**—While in the wards of the hospital, the patient had alternating active diarrhea and constipation. The diarrhea was relatively slight and it was not until he would have two or three movements that the large yellowish-white, foamy stool typical of sprue would appear and usually this would be present only with one passage. Since coming to the medical clinic, he has had several attacks of diarrhea, which are usually always preceded by or associated with soreness of the tongue. The movements, if the diarrhea is at all severe, are typical of sprue. He has had only one or two of these movements until the last two weeks, when he had a sharp recurrence of the symptoms with ten or twelve movements a day, these loose movements lasting for about a week.

**Discussion—Symptomatology**—I should now like to take up with you the symptoms of a case of sprue. The typical, characteristic, text-book picture is that of a patient who is emaciated, pale, with considerable distention of the abdomen and various

gastro-intestinal symptoms, of which diarrhea with the passage of a large amount of extremely offensive, white or fatty, frothy stools is most characteristic. These cases represent a well-developed fully marked, severe case, and, of course, as with every disease, there are marked variations in the severity of the symptoms. Ashford<sup>1</sup> has made the most complete and thorough clinical investigation of sprue of which there is record at least in recent years. He reports on 616 cases examined in his series of 1921. Of these 616 cases 385 were cases of clinical sprue confirmed by the laboratory, 163 were not examined in the laboratory and 68 showed negative laboratory findings. In these cases he found burning of the tongue without demonstrable lesion, or a slight lesion on the tip and edges, or the severe, beefy tongue in 68 per cent. Eighty-six per cent of the cases had acid dyspepsia and 89 per cent had excessive intestinal gas, 120, or 19 per cent, had the typical stool of sprue, 79 per cent had loose bowels going on to diarrhea, at times alternating with constipation. Constipation was noted as an outstanding symptom in 48 per cent of the cases. In the case that you have before you today, you will see that it falls in the category of the large majority of patients, namely, irregular attacks of diarrhea alternating with constipation. Other gastro-intestinal symptoms, such as nausea and vomiting, loss of appetite and heat and burning of the rectum are present in about one-half of the cases. Aside from digestive symptoms, the nervous symptoms are also of considerable importance. These patients are usually irritable and excitable. They suffer from asthenia, sleeplessness, nightmare, various irregular neuralgias, neuritides, and psychic depression. Loss of weight occurs in about 60 per cent of cases and of course, varies with the severity of the disease. In our patient during several attacks the weight went down very sharply. As he gradually improved, the weight went up to approximately what it was before he became sick.

Ashford notes in his cases a rather marked pallor in 56 per cent. He makes no note of blood-counts in his cases, but the occasional occurrence of petechiæ and disturbance of menstrua-

<sup>1</sup> Amer Jour Med Sci, 1923, 165, 157

tion in women, as well as the frequent pallor of his patients, are all indicative of anemia

There is also a tendency to more or less prolonged remissions. In the present case there are exhibited short remissions, while the marked general improvement in the patient suggests the onset of a prolonged freedom from symptoms

*Laboratory Findings*—As far as I can find out, in the severe cases practically always there is development of well-marked anemia, while the majority present the blood-picture of pernicious anemia. This I will discuss with you in a few minutes. The blood-count shows anemia of the red cells and of the hemoglobin, the red cells usually being decreased to a greater extent than the hemoglobin, so that the color-index is over one. The red cells show anisocytosis and poikilocytosis. The leukocytes are correspondingly reduced and the differential count shows relatively slight change. Fragility of the red cells is usually within normal limits, according to C. E. Simon.<sup>1</sup> There is also a tendency to achylia gastrica. The character of the stools I have already mentioned, but it is interesting to note that Ashford has found the *Monilia psilosis* in a very large number of cases and also has found the monilia in the tongue lesions. The patient before you today, on admission to Charity Hospital, presented the typical blood-picture of pernicious anemia. So typical was the picture that the diagnosis of pernicious anemia was made in this case and was maintained some time after his admission to the hospital. Scrapings from his tongue were made several times, but we were unable to isolate monilia in the scrapings. It was not until a few weeks ago that we were able to find the monilia in the stools and successfully cultivate it. Dr. Butler, who found the monilia, reports the characteristics of his cultures as follows:

*Culture of Stools* *Monilia psilosis* (Ashford) or *Monilia enterica* (Castellani) is best isolated on glucose agar plates. Microscopic examination of the stool of Lieutenant D. was made in the ordinary way and the ovoid yeast-like bodies found in great numbers. A thin suspension of the stool was made in

<sup>1</sup> Clinical Diagnosis, Lea & Febiger, Philadelphia, 1922, p. 1057

sterile normal saline solution. A capillary pipet was filled for a distance of 4 or 5 cm with this suspension and emptied into a melted glucose agar tube which had been allowed to cool to about 40° C. Three such tubes had been previously prepared. The capillary portion of a capillary pipet was filled from the first melted agar tube and transferred to a second tube. The same amount was transferred from the second tube to a third tube, thereby making three dilutions. The tubes were thoroughly shaken after each transfer. They were then poured into separate Petri dishes and allowed to cool. The plates were incubated for three or four days, after which time small, round,

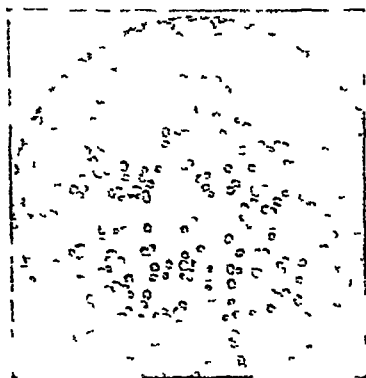


Fig 167—Low-power micrograph of culture of *Monilia psilosis*

elevated, white colonies appeared. They were picked and examined for purity.

In making plates, if the colonies are contaminated, the plating must be repeated until a pure culture is obtained. Subcultures grow best at room temperature. When the culture is pure it is ready for the sugar broths. *Monilia psilosis* produces acid and gas in glucose, galactose, maltose, saccharose, and slight acid in dextrin. It is alkaline in litmus milk, and appears as a heavy white growth on glucose agar slants.

The cultures of yeast cells made from the stools in the present case fulfilled all the above criteria. (See Figs 167, 168.) We therefore have no hesitancy in saying that pure cultures of *M. psilosis* were successfully cultivated.



*Etiology*—I have purposely dismissed the discussion of the etiology of sprue until toward the last, as I wish to discuss this phase of the disease rather fully and to bring out the question also of the relation of sprue to pernicious anemia. Various suggestions have been made as to the causal factor in sprue. It has been spoken of as a deficiency disease, as a disease of glandular insufficiency, as a manifestation of a pancreatic disturbance

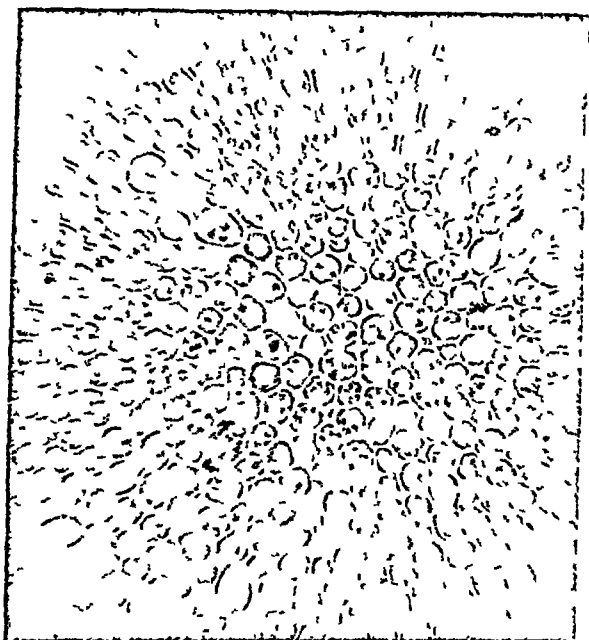


Fig 168—High-power photomicrograph of culture of *Monilia psilosis*

of an inflammatory type, as an infestation with *Strongyloides stercoralis*, and as a combination of several of these factors, while the original theory of Thin was that the disease was due to some specific micro-organism. Extensive study has failed to show any real evidence of micro-organisms being the cause of the disease. Ashford truthfully remarks that the small number of acute cases which develop shortly after the arrival of the patient in Porto Rico from the north and in whom the full sprue syndrome

appears overwhelmingly, show that the disease is not dependent upon food deficiency or glandular insufficiency. Of course, it is impossible to prove from one case anything as to the etiology of the disease, but in this patient we have here today there is no evidence of glandular insufficiency, and his diet has always been that of an active, intelligent man of sufficient means to pay for a full and completely mixed diet. Elders<sup>1</sup> is an enthusiast on the idea of diet having a direct relationship to the disease. It is particularly and undoubtedly true that the majority of patients that he has seen in the East Indies have an improperly balanced diet. The same may be said to hold good of the natives of Porto Rico but the occurrence of sprue in Europeans and Americans who have gone to the Tropics and developed the disease there shows that the diet has no direct etiologic significance. The question of the rôle that yeast plays in the disease has caused a heated discussion in the past few years, but it is not by any means a new problem. In 1901 Kohlbrugge, according to Manson-Bahr, found a large number of yeast cells resembling thrush fungus in the epithelial covering of the tongue and the esophagus. His observations were confirmed by other observers. In 1913 Manson-Bahr says he found yeast cells in tongue scrapings, the intestinal mucus and gastric mucus, postmortem, and fungi were cultured from the spleen, liver, and kidneys. Mycotic development similar to this was not found in other fatal cases of diarrhea. Shortly after this Ashford began to work in Porto Rico and has carried on his work continuously since then, except for the interruption of the Great War. He claims that the monilia found in sprue belongs to a distinct species and he has called it the *Monilia psilosis*. His conclusions are supported by some mycologists and denied by others. Manson-Bahr, in spite of his advocacy of the fungus theory of sprue, is not convinced, however, that the evidence is sufficiently strong to prove the case. He says that the failure to culture the monilia from early cases certainly may point against the yeast as a causative factor and he does not think there are sufficient grounds for considering the *Monilia psilosis* as a distinct species. Castellani considers the mon-

<sup>1</sup> Lancet, January 10, 1925, p 75

ilia as a secondary invading growth in the intestines of the sufferer from sprue, and he likens it to the pathogenic organisms which grow and multiply in the lungs of those affected with pulmonary tuberculosis which bear no relation to the primary disease as a causal agent. Edward Jenner Wood, in this country, is a firm believer in the mycotic theory of the disease, while Bastedo and Famulener<sup>1</sup> say that they are not ready to accept Ashford's theory that the infecting organism is the specific *M. psilosis*, or that it need be any monilia. Other observers, notably in France, could be mentioned who agree and disagree with Ashford's ably maintained thesis. To my mind, the most positive proof is the fact that Ashford has cultivated the monilia in 87.6 per cent of his sprue patients, while only 1.5 per cent of individuals living in the Tropics in endemic zones have been found to harbor the monilia. Somewhat less convincing evidence is the positive complement-fixation test with an emulsion of *M. psilosis* as antigen in a large series of cases.

*The Relationship of Sprue to Pernicious Anemia*—The observation that sprue and pernicious anemia are very closely related is not a new thought, but I confess that it was to me a new idea until I heard the paper of Dr. Wood read before the Southern Medical Association last fall. Since then, in looking up the literature on the subject, I find that it has been observed by numerous students of the disease that there is a very close resemblance between sprue and pernicious anemia. Shortly after I heard the paper by Wood an article appeared in the *Lancet* by Elders<sup>2</sup> advancing very much the same general idea. Thin, according to Elders, was the first to make the observation that the blood-pictures are frequently essentially the same, and he mentions that numerous other observers have found the same thing. Nolen is quoted as saying that it is sometimes impossible to distinguish sprue from pernicious anemia. Ashford<sup>3</sup> writes "I confess myself unable to make up my mind as to what relation sprue bears to an anemia, pernicious in all but the name, and apt to be asso-

<sup>1</sup> Jour Amer Med Assoc, 1923, 81, 2102

<sup>2</sup> January 10, 1925, p. 75

<sup>3</sup> Ann Clin Med, 1925, 4, 13

ciated, as it is, with achylia gastrica. That a large number of cases of sprue end fatally with a blood-picture indistinguishable from that of pernicious anemia is incontrovertible. I have blood-slides with histories that should be convincing. I wish to record one case of uncomplicated sprue with 512,000 erythrocytes per cubic millimeter and 14 per cent hemoglobin."

As keen a clinical observer as Dr E. Libman,<sup>1</sup> in discussing pernicious anemia before the Association of American Physicians, said that in the earlier meetings of the Association he had stressed the importance of a comparative study of the two diseases, and that to him the toxic agents of these diseases seemed analogous in their action. Wood has carried the argument of the duality of the two diseases even further, and has presented some very convincing evidence and arguments in favor of the fact that sprue is a possible type of pernicious anemia. Elders is thoroughly convinced that the two diseases are closely related, but he argues from a point of view which to me seems fallacious, namely, that they are both deficiency diseases and the differences when they do occur are simply manifestations of the same disease. Elders, in his article, gives the full blood-counts of 3 cases of sprue and shows that the blood findings are absolutely typical of pernicious anemia. He says further that nearly all the clinical peculiarities of pernicious anemia are found in tropical sprue. It is obvious from his blood-counts and the reports of others that this is true. In sprue there is a high color-index which is particularly marked when the patient is severely ill and when the anemia is most pronounced, and it gradually approaches normal as the red cells and hemoglobin approach normal. Wood attributes a somewhat different pathogenesis to the two diseases, namely, that *Monilia psilosis* is the probable cause of sprue. He has been able to isolate this yeast in cases of pernicious anemia. In the discussion of Wood's paper before the Southern Medical Association the point brought out by Dr Fontaine, of Memphis, seems to be the best argument against the duality of the diseases, namely, that there is not necessarily achylia gastrica in cases of sprue, while this is a finding which is con-

<sup>1</sup> Jour Amer Med Assoc., 1925, 84, 1869

patients several pounds of underdone meat a day, 2 liters of raw milk, small doses of cod-liver oil, and oranges or strawberries. Incidentally, the so-called strawberry cure was one of the first cures used for the disease. The patients take 2 to 3 pounds of them a day.

In Lieutenant D's case we have forced milk and have given *Bacillus acidophilus* milk for the usual reasons that this milk is administered and it has worked very well indeed. A day or two of fasting except for the milk will relieve any diarrheal attacks. It has not, however, caused monilia to disappear from the stools, nor do I believe that it will. In addition to his dietetic treatment, consisting largely of proteins and fresh fruit, we have combated his anemia with intramuscular injections of arsenic and he has taken iron by mouth.

Summary—I have attempted today to show you the close relationship that exists between sprue and pernicious anemia, to stress the clinical manifestations of sprue, and to present to you the results of treatment seen in a case of sprue.

# CLINIC OF DR L R DEBUYS

## TOURO INFIRMARY

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### A CHRONIC NEPHRITIS (HEMORRHAGIC)

**Case History**—Walter L, a white male child, age seven years, weighing 45 pounds, was admitted into my service at the Touro Infirmary on February 18, 1925 with the complaint that he had been passing blood in his urine

He was the son of healthy parents, both of whom were twenty-eight years of age, and had a sister three years old who was also well. The family history was negative with the exception of a miscarriage at three and a half months of the pregnancy between the pregnancies of Walter and his sister.

It was said that Walter weighed 12 pounds at birth and was delivered in a normal manner. He was breast fed exclusively for five months, when condensed milk was added to his diet. After the eighth month other foods were added without causing any disturbance. He had his first tooth at four months, walked at thirteen months, and talked at about the same time. He had no infectious diseases before the blood was first noticed in his urine at the age of fifteen months. At two years of age he had measles and whooping-cough, and at four years he had mumps. He had had no other ailments. There was no history of pain referable to the genito-urinary tract at any time.

When fifteen months old his mother first noticed that his diapers would be blood stained. This condition grew steadily worse. He had made the round of doctors and other clinics and visited the Out-patient Department of the Touro Infirmary where it was advised that he be admitted for observation.

Upon admission Walter was found to appear to be anemic though he was well developed and nourished. His physical examination was negative, with the exception that his tonsils were somewhat enlarged, his nasopharynx slightly reddened, and there was some evidence of impaired hearing. This latter condition dated from his measles when he had had abscesses of both ears. His teeth and lymphatic glands were also negative. His blood-pressure 96/46.

The laboratory findings were as follows:

Blood Hemoglobin, 45 per cent, total red blood-cells, 4,850,000, total white blood-cells, 4500.

Differential count: Small mononuclears, 35 per cent, large mononuclears, 2 per cent, polymorphonuclears, 54 per cent, eosinophils, 8 per cent, basophils, 1 per cent. No malaria plasmodia. Color-index, 0.46, platelet count, 280,000.

Blood Wassermann negative

Coagulation time, three minutes, fifty seconds

Stool examination was negative as to digestive disturbance and for parasitic infection

Urine examination Color, light straw with reddish-brown sediment, specific gravity, 1011, reaction acid, albumin less than 0.5 per cent, sediment, occasional granular cast and blood-cast, hyaline casts, many red blood-cells, and few leukocytes. Otherwise the urine was normal

Blood chemistry Total non-protein nitrogen, 39 mg per 100 c.c., urea nitrogen, 19.5 mg per 100 c.c., creatinin, 1.3 mg per 100 c.c., uric acid, 5.50 mg per 100 c.c., dextrose, 88 mg per 100 c.c.

Phenolsulphonaphthalein test showed

First hour, 35

Second hour, 20

55

Mosenthal diet showed a variation in flexibility of 16 points. Von Pirquet and intradermal tuberculin reactions were negative

Schick test was positive

Dick test was positive

Nose and throat culture negative for diphtheria

*Consultations* 2/19/25 Roentgenographic examination of genito-urinary tract without any injections was reported to be negative by Drs E. C. Samuel and E. R. Bowie

6/4/25 Roentgenographic examination of sinuses and mastoid region was negative

2/20/25 Examination of eyes by Dr M. Feingold. Eye grounds negative. Examination of ears, nose, and throat by Dr A. I. Weil. Ears normal, nose normal. Throat. Tonsils moderately enlarged and show slight evidence of disease. Fair sized adenoids.

6/6/25 The tonsils and adenoids were removed under ethylene (70 to 75 per cent). Duration of anesthetic twenty minutes.

6/22/25 Cystoscopic examination of genito-urinary tract under ethylene was made by Dr A. Nelken. It showed bladder and pelvis of kidney to be negative, and specimen from both ureters showed both kidneys functioning slowly and urine containing red blood cells. Cultures negative. The patient was discharged from the Infirmary on 8/18/25. His weight on this date was 51 pounds.

**Comment**—During the period of his stay in the hospital the various tests were repeated from time to time, and in the main they were practically the same, so that those given expressed the average. Some items of interest may be mentioned in connection with the progress of the case. After excluding the various foci of possible infection, with the exception of the tonsils, it was decided to have them removed. Consequently, this was done

and without any unusual disturbance to the patient. This had no effect upon the hematuria which continued in the same amount. Believing the bleeding was from the kidneys we were reluctant in giving a general anesthetic because of the nephritis. He took the general anesthetic so well, however, that shortly thereafter he was given a general anesthetic again for a cystoscopic examination. He went through this ordeal also uneventfully. He was not given any opaque injections for roentgenographic observation because of the belief of the source of the bleeding and the possible hazard if the surmise with regard to the bleed was correct. The result of the cystoscopic examination confirmed our suspicion as to the origin of the hemorrhage, as there was nothing in the urethra or bladder, and the blood was found in the urine obtained from the ureters upon their catheterization. There were at no time casts the size of the ureters, but, on the other hand, the casts were the size of the usual blood-casts of kidney origin. Our conclusions, because of these findings, the history of no pain, negative Roentgen-ray findings, and negative physical findings, therefore, was that the bleeding was from the kidney.

The various drugs to increase coagulation and arrest hemorrhage were tried without effect, and he was transfused with 300 c.c. of his father's blood given by the direct method. This resulted in a decided diminution in the amount of blood in the urine, but by the following morning his urine was just as bloody as it had been. The amount of blood in the urine was markedly increased the second day, being more than it had been at any time. This was only transient, however, as the next day the blood in the urine had returned to its usual amount.

**Discussion**—In attempting to arrive at the cause of the hematuria in this particular instance the following conditions must be considered: (1) Drugs, (2) toxins, (3) infections, (4) tuberculosis, (5) syphilis, (6) malaria, (7) new growths, (8) blood dyscrasias, (9) mechanical causes, (10) kidney disease.

1. Drugs could be definitely excluded, as there was no history of the giving of drugs, and the case was under observation sufficiently for the effect of any drug to have entirely disappeared.



2 Toxins could be excluded, (a) because all the known causes for the presence of toxins were excluded, (b) because all the organs of elimination were functioning normally, and (c) the patient did not appear toxic.

3 Infections both acute and chronic were excluded

The immediate causes of acute infections were excluded because (a) of the physical examination, (b) of the duration of the hematuria, (c) of the absence of disturbance in temperature, pulse, and respiration, the remote causes of acute infections because (a) of the history, (b) the positive Schick and Dick tests, (c) the attack of measles followed the onset of the hematuria

The chronic infections were excluded by (a) the physical findings, (b) the absence of evidence of a chronic drain on the patient, (c) the general improvement of the patient while under observation even while the hematuria continued unabated

4 Tuberculosis was excluded by the (a) history, (b) physical examination, (c) laboratory findings, (d) by the tuberculin reactions which were negative While a positive reaction may become less reliable as a diagnostic measure as the age of the individual advances, a negative reaction is always of value

5 Syphilis was excluded by the (a) family history, (b) history of the patient, (c) negative Wassermann, (d) adequate therapeutic test

6 Malaria was excluded by the (a) history of the case, (b) physical examination, (c) negative blood findings

7 New growths were excluded by the (a) history, (b) duration of the illness, (c) absence of tumor of the kidney, and of the bladder upon cystoscopic examination Tumor of the kidney is a condition practically unknown in a child, and tumor of the bladder, though one of the most frequent of the abdominal tumors in the child, has a typical clinical picture which was absent in this instance

8 Blood dyscrasias were excluded upon the blood findings and the clinical history of the case

9 Mechanical causes in the urethra, bladder, ureters, and pelvis of the kidney were all excluded by (a) cystoscopic, (b) Roentgen-ray examination, (c) the history of absence of pain

10 Finally, kidney disease must be considered, and it cannot be ruled out because the hemorrhage has been shown to be of renal origin. Again, the increased protein and uric acid in the blood and the presence of casts (both hyaline and granular) in the urine with albuminuria are conclusive evidence of a nephritis. The presence of blood-casts indicate that some of the bleeding at least is coming from the kidneys, but since all other sources of bleeding of the urinary tract have been excluded the kidneys alone are to be blamed for the hematuria.

The hemorrhage has not been a paroxysmal or periodic affair, and should not be looked upon as a renal hemophilia or renal epistaxis, but it has been a chronic continuous bleeding for five and a half years. Much blood may be present in the urine in acute diffuse nephritis, and also copious hemorrhages may occur occasionally in granular kidney, but these hemorrhages are not to be compared with the hemorrhage in this case both as to persistence and duration.

Whether the hemorrhage antedated the other positive findings or followed them it cannot be said, as there were no complete examinations made at the beginning of the disease. The absence of cardiovascular changes, uremic symptoms, retinal changes, and edema are of interest in this case.

In conclusion, the case is one of nephritis, chronic in character, with hemorrhage as its outstanding symptom, therefore a chronic nephritis (hemorrhagic).



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## DENGUE FEVER, WITH SPECIAL CONSIDERATION OF THE ETIOLOGY AND TRANSMISSION

THE appearance of dengue fever in epidemic form in the United States, though occurring at intervals of one or more decades, is of interest to the medical profession, and particularly the physician of the far South because, almost without exception, the visitations of the disease have occurred in this locality. Since dengue fever is of rather unusual occurrence in this country and rarely presents itself for clinical study in hospitals, we believe that a presentation of a clinic based upon our clinical and research experiences which were afforded by the late epidemic here at New Orleans may prove of interest and value. While dengue is rarely attended with mortality, when unrecognized or not diagnosed it may cause considerable anxiety to the physician in attendance because sometimes the symptoms simulate grave maladies, such as yellow fever, influenza, and measles. Where the disease has occurred concomitantly or subsequent to yellow fever in the same locality, undoubtedly cases of dengue have been wrongly diagnosed and treated as yellow fever and recorded as recoveries. In this connection it is pertinent to state that the last epidemic of yellow fever in Louisiana (1905) was said to be followed by an outbreak of dengue. Whether or not such was the case cannot be determined from the records. It is possible that the febrile cases following in the wake of yellow fever were mild forms of the latter, and not dengue or another disease entity. We believe that not enough attention has been paid to the differential clinical features of these two diseases which

might explain, in part at least, the confusion heretofore experienced in the diagnosis of yellow and dengue fevers. It is noteworthy that the "rash" and leukopenia are rarely ever absent in dengue fever, and in our experience present in fully 98 per cent of cases, while these pathognomic signs never occurred in yellow fever, even in mild cases of the disease, as far as we can determine.

Dengue fever is an acute infectious febrile disease occurring in epidemic form in tropical and subtropical countries. Endemically it is a disease of the tropics, prevailing in the Philippine Islands, Porto Rica, and certain parts of equatorial South America. In the United States epidemics of dengue have occurred as far north as Virginia (1888), but have usually appeared in the Gulf States. It is especially noteworthy that for no scientific reason the disease has appeared as a forerunner, concomitantly with, or in the wake of, yellow fever visitations. This fact perhaps more than any other led some clinicians to regard the disease as a mild type of yellow fever, particularly as certain cases of dengue are associated with mucous membrane hemorrhages and jaundice.

Dengue fever is called at times break-bone or dandy fever break-bone because the pains are often terrific, feeling as if the bones are breaking, and dandy fever because it occasions in many instances a stiffening of the joints which is noticeable upon walking, and suggests a dandified gait.

The incubation period of this disease as demonstrated by the blood transmission experiments in the human by Ashburn and Craig,<sup>1</sup> Chandler and Rice,<sup>2</sup> and also by those who carried out successful mosquito transmission experiments, as well as the experimentally induced disease in the lower animals by ourselves,<sup>3</sup> determined conclusively that the average is three days.

**Symptomatology**—The symptoms of dengue fever are rather striking and significant because of their severity and suddenness. The disease is ushered in commonly with a chill, fever, and intense pains over the body and a feeling of oppression. The febrile chart may present two aspects either a sudden rise ranging from 101° to 104° F, which lasts for four to six days, and

then subsides, or the temperature may present the so-called saddle-back curve, *i e*, a primary rise of several degrees lasting two to four days, then an intermission lasting from several to twenty-four hours, rarely longer, followed by a secondary rise, having a duration of twenty-four to seventy-two hours. This second elevation of the fever is usually milder than that of the primary rise, however, the secondary pyrexia may be more severe than the primary.

The pains are of an intense character and are usually located in the head, neck, back, and extremities, including the joints. The head pain may be general or confined to the region of the orbits. Those in the body and extremities are at times so intense as to render lying in bed very difficult. The joint pains are occasionally accompanied by redness and swelling. Hyperesthesia of the skin may occur. The pains are notably intensified by motion of the affected part.

Early in the disease with the onset of fever the exposed surfaces of the body especially present a blush or erythema. At this time suffusion and injection of the conjunctiva and nasopharyngeal mucous membrane often occurs. The erythematous condition of the skin of the face must not be confused with the rash or exanthem that occurs later and is one of the characteristics of the malady. It appears to us that the early erythematous condition described by some as the true eruption of dengue fever is nothing more than the ordinary pyrexial blush. In our experience with the epidemic here in New Orleans the "rash" appeared on the second or third day after the onset of the fever and was characterized by slightly elevated pinhead and larger maculopapules, not unlike in color, size, and consistency the roseola of typhoid fever. As to the location of the true exanthem, it appears more often on the face, neck, shoulders, chest, flexor surfaces of the arms, forearms, and the anterior aspect of the thighs. The "rash" may spread to other parts of the body and in some cases become generalized. Even where general and regarded as typical the individual lesions are discrete. The eruption is usually evanescent, lasting at most two or three days, and is not followed by desquamation. At the onset

of the disease there are frequently symptoms referable to the upper respiratory tract which are strikingly like those of influenza and measles, that is, there occurs suffusion of the eyes, injection of the conjunctiva, nasal and pharyngeal mucous membrane. Often the patient has a dry cough and complains of photophobia. As this occurs early in the disease, before the appearance of the "rash" and the leukopenia, one can readily appreciate how it may be mistaken for influenza or measles.

Gastro-intestinal symptoms in dengue are not prominent, although nausea and vomiting occur in certain severe cases. During the epidemic here in New Orleans we encountered but one case which presented black vomit. This case also had intense jaundice, and its analogy to yellow fever under such circumstances can be understood. Hemorrhages from the various mucous membranes have been reported in other epidemics of dengue. Jaundice was seen in less than 1 per cent of the cases in Louisiana's recent epidemic. One case in particular which was used for experimental etiologic study presented intense jaundice.

Enlargement of the superficial lymph-glands and spleen is a common occurrence in dengue fever. In the experimental animal in which the disease was considered to be induced there did not occur jaundice or hemorrhage upon mucous membranes, however, like for the human disease, glandular and splenic enlargement was a characteristic feature. So frequently did this pathology occur that we regarded it as significant of the experimentally induced disease.

In conjunction with the previously described symptomatology one of the most constant aids in the diagnosis of dengue fever is the decrease of the white cells of the circulation. The leukopenia considered with the "rash," pyrexia, and deep-seated pains are clinically pathognomonic of the disease. The reduction of the total leukocytic count may not be observed on the first or second day of the disease, but sooner or later during the course of the infection leukopenia will become evident. Usually with the fastigium, when the febrile reaction is at its height, the leukocytic depression is most marked. As the infection abates there is a gradual return of the leukocytic count to normal. In

our transmission experiments to the lower animals this leukocytic reduction in conjunction with the febrile reaction was a most striking and significant feature. The depressant effect of the virus of dengue upon the leukocytes could be better appreciated in the lower animal, particularly the guinea-pig, because of the higher normal leukocytic level (10,000 to 12,000). In this animal reduction in the white cells to 3000 was frequently observed.

The results of blood-cultures upon the ordinary laboratory media have been reported negative by nearly all investigators. Those carried out by us upon specialized media will be discussed under etiology.

**Clinical Cases**—As it is impractical to present in detail a large number of cases, we will only enumerate a few that we regard as representative of uncomplicated dengue fever. These cases among others afforded our material for experimental study of the transmission to lower animals and the incentive for etiologic study.

**CASE I**—An Italian girl, aged sixteen years, gives a history of her present illness having been ushered in three days ago with a chill, followed by intense frontal headache, high fever, and severe pain over the body, more particularly the back and lower extremities. The following day patient states that the pains became more general, and were made worse on motion of the affected parts. When first seen by the attending physician, the second day of illness, her temperature was 104° F. On the third day of the disease the patient showed photophobia and a drop of 1 degree in the temperature, pains not so severe on motion. Concomitantly with the recession in temperature there appeared a roseolar eruption on chest, arms, and face. On this date 15 c.c. of blood were withdrawn from the medium basilic vein, defibrinated, and portions used to inoculate animals and special culture-media. Four days after the onset of the illness the temperature was 101° F., the total leukocytic count 3000, and the rash at its maximum intensity. On the fifth day the rash began to fade, and by the sixth day had entirely disappeared. After the appearance of the rash the patient no longer complained of pain. The febrile chart of this case did not present the characteristic saddle-back curve. The blood from this patient induced in the experimental animal a febrile and leukocytic response analogous to that which occurred in the human.

**CASE II**—A white boy, aged eleven years, was perfectly well prior to present illness, which began suddenly with chill, followed by high fever,



headache, photophobia, and cramp-like pains in the arms and legs. On the second day of the disease the temperature was  $103^{\circ}$  F and the leukocytic count 4500. At this time the patient complained of aches and pains over the entire body, but more severe in the back of the neck (occipital). The rash, macular in character, appeared over the legs and arms on the third day of the illness. The temperature was normal and the eruption fading on the fourth day. For this case there was no secondary rise in temperature, patient made a rapid recovery and was perfectly well after an illness of one week. Blood was obtained from this case for experimental study on the second day of the disease.

**CASE III**—A white man, aged twenty-six years, was stricken suddenly and complained at the onset of illness of burning sensation in the eyes and pains in the back, arms, and legs, which, as patient described, seemed to be in his very bones. The doctor who saw him that same day found his temperature  $102^{\circ}$  F, and the following day noted that patient's forehead, chest, and arms were dotted with a discrete roseolar eruption. On this day the patient was greatly prostrated and visibly sick. The leukocytic count was 3250 and the temperature  $104^{\circ}$  F. Twenty c c of blood were withdrawn from the vein at the bend of the elbow and a part placed in 2 per cent citrate, and another portion defibrinated and Berkefeld filtered. The citrated and filtered bloods were used for cultural study and animal inoculation. This patient made an uneventful recovery after an illness of seven days. The rash disappeared on the fifth day, or two days after its appearance.

**CASE IV**—A male, aged thirty-two years, native of New Orleans, had enjoyed good health until time of attack. Headache and general malaise were experienced on the morning preceding the illness. In the afternoon of the same day patient was stricken on the street and taken home in a dazed condition. Pulse at this time was weak and there was great prostration. On the next day the temperature rose to  $104^{\circ}$  F, and patient complained of severe pains and aches over the body. Fifty hours after the onset of the disease the temperature was  $103^{\circ}$  F and the leukocytic count 4000. On the third day of illness the patient broke out in a typical roseolar eruption which lasted two days. This case had a secondary rise in fever four days after the onset of illness which followed a remission of the temperature to normal. Blood was withdrawn from the arm vein for experimental study at the time when the rash was at the peak. Ten days after the onset of illness this case was entirely well.

**CASE V**—A married woman, thirty-eight years of age, native of Italy, residing for past ten years in New Orleans was seized suddenly with chill and fever, followed by headache and severe pains in abdomen and legs. This patient was admitted to hospital on the sixth day after the onset of the disease. At time of admission patient was markedly jaundiced, complaining of nausea and pains in the bones of the lower extremities. On this date the eruption was fading and the temperature was  $103^{\circ}$  F, leukocytic count 4000. Patient states that rash appeared two days previous to her admission to

hospital Blood was removed by venipuncture for experimentation During the course of the disease the temperature of this patient described the typical saddle back curve The jaundice persisted for a week or more after the fever had subsided Case made an uneventful recovery

CASE VI—A white female, aged thirty-six years, was a native of New Orleans Her illness began with chill and fever followed by pains in the back and severe headache The temperature remained around 104° F for two days, fell to normal on the third day, to rise again to 101° F on the day following A roseolar eruption appeared during the secondary pyrexia and persisted for forty-eight hours The leukocytic count on the fourth day of the disease was 3500 Blood was collected from the arm vein on the second day of illness

CASE VII—Female, aged eighteen years, native of New Orleans Illness began suddenly with a chill, followed by fever of 104° F Patient complained on first day of illness of severe headache and pains in the back and extremities On the third day of the disease a characteristic roseolar eruption appeared on the face and chest and faded rapidly two days later There was no marked remission of the fever during the eight days of illness The total leukocytic count in this case remained around the normal throughout the period of the disease Patient was bled on the fourth day of the disease and 12 c c of blood removed for experimental study

CASE VIII—Female, aged twenty-four years, the onset of the disease was ushered in with chills, headache, and pain in the back and lower extremity On the first day of illness there was noted marked injection of the conjunctiva and coryza The temperature was 103° F, rash appeared generally over the body on the second day, and was of a macular variety The leukocytic count was at no time lower than 5000 The temperature ranged between 101° and 103° F throughout the period of illness, which was five days Twenty c c of blood were obtained for study on the second day of the illness

Mosquito Transmission—It is now generally recognized that the mosquito is the intermediate means through which dengue fever is transmitted Varied results, however, have been obtained from experiments carried out along this line Graham<sup>4</sup> in 1903 was the first to show that dengue is transmitted by the bite of the mosquito He transported mosquitos which had fed upon dengue patients to a remote area where dengue did not exist, and succeeded with them in infecting human volunteers He also considered that he had produced a very severe case of dengue fever by inoculating a man sub-

cutaneously with a peptonized normal salt solution containing the salivary glands of a mosquito (*Culex fatigans*) which had bitten a dengue patient twenty-four hours previously. Carpenter and Sutton<sup>5</sup> obtained two positive results out of four experiments with mosquito inoculation. The incubation period, however, was two weeks, and the subjects were not sufficiently controlled. Agramonte,<sup>6</sup> in Havana, studied an epidemic of dengue during which great numbers of *Culex fatigans* prevailed. His efforts at transmission with the mosquito proved negative. Guiteras and Finlay<sup>7</sup> likewise obtained negative results with the *Culex pipiens*. Bancroft<sup>8</sup> succeeded in transmitting dengue by means of the *Stegomyia fasciata*, though his experiments were performed in an infected area, which vitiates the reported results. Ashburn and Craig,<sup>1</sup> in their attempt to confirm Graham's mosquito transmission work, report 1 doubtful case in 9 bitten by the *Culex fatigans*. Cleland, Bradley, and McDonald<sup>9</sup> collected *Stegomyia fasciata* (*Aedes ægypti*) from the room of a dengue fever case. Some of these insects were known to have fed upon the patient with the disease. These infested mosquitos were carried to a non-infected dengue area where they were allowed to feed upon non-immune human volunteers. They produced dengue in 4 out of the 7 volunteers used in the experiment. It is noteworthy that no new cases developed in this area. Their experiments with *Culex fatigans* were negative. These authors secured blood from the cases of the disease experimentally produced, and by means of subcutaneous injection into non-immune volunteers occasioned dengue fever.

Chandler and Rice<sup>2</sup> in 1923, during a scourge of *Stegomyia fasciata* (*Aedes ægypti*) occurring in the same epidemic of dengue in which we were interested, carried out mosquito transmission experiments. They succeeded in transmitting the disease in 4 out of 7 instances. Their work was, however, performed in a prevailing epidemic area, although they state that every care was exercised to prevent vitiation of the results by proper screening and other methods of precaution.

In the present year (1925) Siler, Hall, and Hitchens,<sup>10</sup> working in Manila, state that their mosquito transmission experi-

ments indicate that the *Stegomyia fasciata* or *Aedes ægypti* is the agent of transmission for dengue fever, whereas the *Culex quinquefasciatus* or *fatigans* plays no part in the transmission of the disease. Their experiments, while carried out in an epidemic area, were conducted along a carefully arranged plan whereby they considered that possible outside infection could be eliminated.

Up to the present time the experiments which have been carried out for mosquito transmission of the virus of dengue has not definitely established a particular species. Whether it is the *Aedes ægypti* or some other species that is the mode of transmission is yet to be determined, since the results of workers in this field are at variance. The results as a whole, however, indicate that the probable conveyor of this infection is the *Stegomyia fasciata* or *Aedes ægypti*. Regardless of which species transmits dengue fever, it has not been shown whether the mosquito is a simple mechanical carrier of the virus or is a true definitive host. Based on experiments Siler, Hall, and Hitchens<sup>10</sup> claim that the virus of dengue has a developmental period of eleven days in the *Aedes ægypti* before it is capable of infecting man. This mosquito, according to these authors, remains infectious for the rest of her life. In other words, they consider that the mosquito is a definitive host for the dengue virus. Their results with the *Culex quinquefasciatus* were negative. Bancroft<sup>8</sup> previously found in experiments with the *Stegomyia fasciata* or *Aedes ægypti* that positive transmission occurred with mosquitos that had fed on dengue patients ten to twelve days previously. His results with mosquitos that had fed fifteen and seventeen days before on dengue patients were negative. Ashburn and Craig<sup>1</sup> obtained contrary results both as regards the species of mosquito and the period of time at which infection of the human was possible. These authors state that they obtained conclusive evidence that the disease is transmitted by the *Culex fatigans*. They also state that the positive results were obtained with mosquitos that had fed upon dengue patients only forty-eight hours previously. Chandler and Rice<sup>2</sup> recently determined that the *Stegomyia fasciata* or *Aedes ægypti* is the

mosquito concerned in the transmission of the disease and is capable of infecting in twenty-four to ninety-six hours after having fed on the blood of dengue patients

The work of others with the human disease and our own experience with the experimental animal show conclusively that dengue fever is not directly transmitted from human to human, but requires some intermediate means of inoculation

**Etiology.**—With regard to the search for the causal excitant of dengue fever a number of investigators have experimented, and their results either have been negative or, where positive, have remained unconfirmed. Graham<sup>4</sup> in 1903 observed within the corpuscles of the circulating blood of human dengue cases peculiar bodies which he regarded as protozoal parasites. He also observed the same bodies in the stomach of the *Culex fatigans* which had previously been allowed to feed on the dengue fever patient. The finding of similar bodies in the mosquito led him to believe that he had discovered the causal agent of the disease. Although the parasitic nature of Graham's corpuscular bodies are questioned, credit is due him through his mosquito experiments for first calling our attention to the existence of the dengue virus in the circulation during the febrile stage of the disease. The existence in the circulating blood of the specific agent and its filtrability through earthen filters that retain *Bacillus melitensis* and *Vibrio cholerae* were conclusively demonstrated by Ashburn and Craig in 1907. Couvy<sup>11</sup> reports the finding of spirochetal organisms in the blood of dengue fever prior to the onset of the febrile reaction, but not after the pyrexia was established. Verwort,<sup>12</sup> from Sumatra, also reports the finding of spiral organisms in the blood of dengue fever patients.

Like other workers, we considered that some spirochetal form might possibly be the etiologic factor in dengue because of the prevalent opinion that the disease is allied to yellow fever whose leptospiral etiology has been discovered by Noguchi.<sup>13</sup> However, we have been unable, after careful and painstaking search of the blood from human dengue in various stages of the disease, and blood from the animal in which the disease was

experimentally induced, to demonstrate any true spirochetal organism. Likewise no such organism was observed in the special cultures prepared with the dengue blood. It may be stated in this connection that in dark-field work upon dengue blood and cultures that the filamentous red blood-cell extrusions may be mistaken for parasites because of the great similarity in morphology assumed by these artefacts. At times and under certain conditions these erythrocytic filaments are extremely numerous, especially in old blood and in cultures where blood has been used. Careful studies of these filaments show them protruding and attached to the red blood-cells. They increase in length while still attached, and later are mechanically separated, floating away in the medium as free filaments of varying sizes and shapes. These spiral forms and their molecular movement may closely approach the morphology and locomotion of true spirochetes. The fact that only a few of these filaments were observed in the fresh blood of the human case and in great numbers in special culture-media led us to consider them as possible living organisms. We were relieved to know from our colleague, Dr Bass, that he had likewise observed these erythrocytic artefacts in certain dark-field work in connection with malaria and other bloods. Later we had no difficulty in demonstrating the same red blood-cell filaments in normal withdrawn blood. Schultz<sup>21</sup> and Noguchi<sup>13</sup> have pointed out the existence of these erythrocytic thread-like extrusions in all drawn bloods, and their similarity to well-known spirochetes. Others besides ourselves who have investigated by means of the direct and cultural methods the blood of dengue for the specific purpose of detecting a possible leptospiral organism, doubt the contention claimed by some that true spirochetal forms occur in the blood of dengue fever patients.

The discovery by Noguchi of a leptospira in yellow fever led Craig<sup>14</sup> among others to predict that dengue was most likely due to a similar organism. Craig based his opinion upon the following points of similarity for the two diseases. Both diseases are caused by a filtrable micro-organism, they are transmitted from host to host by means of a mosquito, probably

the same species, the diseases are frequently associated in concurrent epidemics, and at times the clinical aspect of dengue closely approaches that of yellow fever. Craig further believed that work along similar lines for dengue as was carried out by Noguchi<sup>13</sup> for yellow fever would reveal some spirochetal form of organism as the causal excitant of the disease. For the same reasons we thought it likely that some spirochete related to the leptospira might be found in dengue fever. Our work and that of others directed along this line have satisfied us, however, that no such micro-organism is the cause of dengue fever.

Chandler and Rice,<sup>2</sup> Siler, Hall and Hitchens,<sup>10</sup> and ourselves<sup>15 16</sup> have carried out etiologic studies, using Noguchi's methods for cultivating highly parasitic organisms. Repeated dark-field examination of the fresh blood of dengue patients at various stages of the disease, frequent dark-field examination of blood-cultures on the special media devised by Noguchi, and, in our own work, the same procedures upon the experimentally induced disease in the guinea-pig, have constantly failed to reveal any true spiral organism. In other words, since experimental investigations have been directed specifically along lines calculated to disclose a spirochete, it seems likely that if such was the cause it would have been brought to light.

The only bodies found by us which in any manner simulated spirochetes were the red blood-corpuscle protoplasmic filaments which have already been alluded to. Hall<sup>17</sup> very recently described the finding of the same filaments in the blood of dengue patients, and he likewise realized that they were of no etiologic significance. In the work of Couvy<sup>11</sup> and Verwort<sup>12</sup> upon the etiology of dengue the spiral organisms described seem similar to these red blood-cell artefacts. It is also to be noted that their observations were always made upon materials containing red blood-cells. Verwort found in his cultures that the addition of laked blood was essential for subculture. This in itself suggests the origin of his spirochete to be that of the erythrocytic cell, as it has been shown by Noguchi that all

known forms of leptospira will perpetuate in serum and plasma alone

When it was appreciated by us that a complete investigation for the possible existence of a leptospira in dengue fever yielded only negative results, we approached the subject from a broader prospectus, endeavoring to find any form of micro-organism that might be present. Our experimental studies consisted of two divisions: first, to obtain from the blood of dengue patients a micro-organism responsible for the disease which was carried out both through direct blood examinations and special cultural methods. Second, the inoculation of blood from dengue fever patients into the guinea-pig for the purpose of transmitting the disease. Having succeeded in inducing a specific reaction in these animals, we were afforded thereby a supply of dengue virus material.

From such cases of dengue as herein described, and from many of the guinea-pigs wherein the experimental disease had been transmitted, numerous dark-field examinations and smear preparations were made with the view of detecting any protozoal bodies. Our efforts through these means yielded only negative results. It was considered that cultural examination would more likely prove of avail. Although the culture-medium generally used for routine blood-cultures was employed, our efforts were especially directed to the usage of the media devised by Noguchi for the cultivation of spirochetes and the virus of poliomyelitis. Repeated cultures were made from the human cases and the infected guinea-pigs, but no micro-organism consistent with those generally known could be found.

In cultures upon these specialized media, however, minute coccoid bodies were occasionally found, occurring in colony-like masses, as diplococci and as short chains. It was at first thought that these bodies were particulate matter derived from the materials of the special food-stuff. As distinct colonization was later shown in the culture-tubes, these bodies were studied more critically, and finally considered to be a true living micro-organism. These globoid "bodies" are very similar to those cultivated by Flexner and Noguchi<sup>18</sup> from poliomyelitis. They



are minute "coccoids" measuring from 0.1 to 0.3 microns in diameter which readily pass the V and N Berkefeld filter. They do not stain by Gram's method or the simple dyes with the exception of carbolfuchsin. The various Romanowski methods of staining, particularly that of Giemsa, define more clearly this minute organism. In regard to the usage of highly specialized protein media we recalled that Dr J V Cooke, while working in these laboratories in 1912 upon the cultivation of the virus

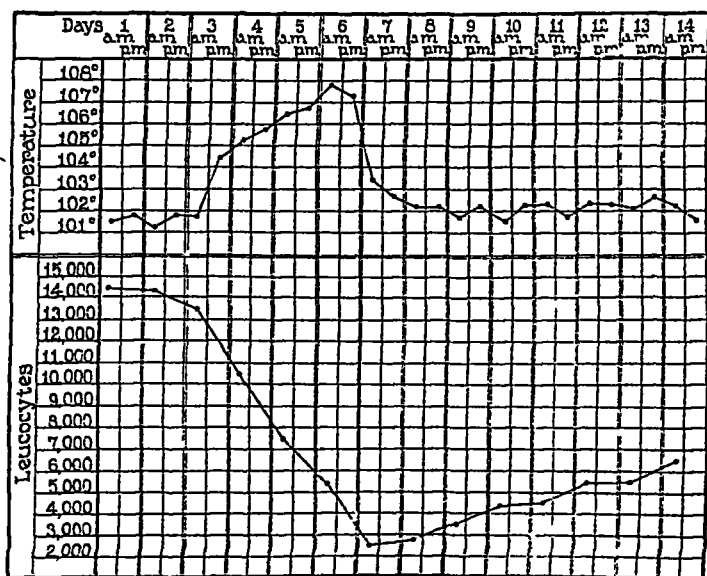


Fig. 169 — Experimental dengue in the guinea-pig

of polyomyelitis, observed artefacts simulating bacterial colonization not only in his virus-inoculated tubes, but also in the uninoculated controls. The work of Laidlaw<sup>19</sup> and Twort and Twort<sup>20</sup> has also called attention to this possible pitfall. These latter workers regard certain of the minute bodies and their colonization in highly specialized protein media as crystallization processes in which calcium and magnesium salts combine with fatty acids to form soaps. We have carefully considered and compared these artefacts both in smear and "colony," and it

is our belief that the globoid bodies for dengue fever are animate structures or true living micro-organisms. Subcultivation of our globoid bodies was successful through several generations, but as the cultures would eventually die out, it is further indicative of viability. If their occurrence and colonization were due to physical or chemical phenomena, their perpetuation should have been unending. The cultivation of these globoid bodies was possible both from the blood of the human case and the experimental animal. Their inoculation into the lower

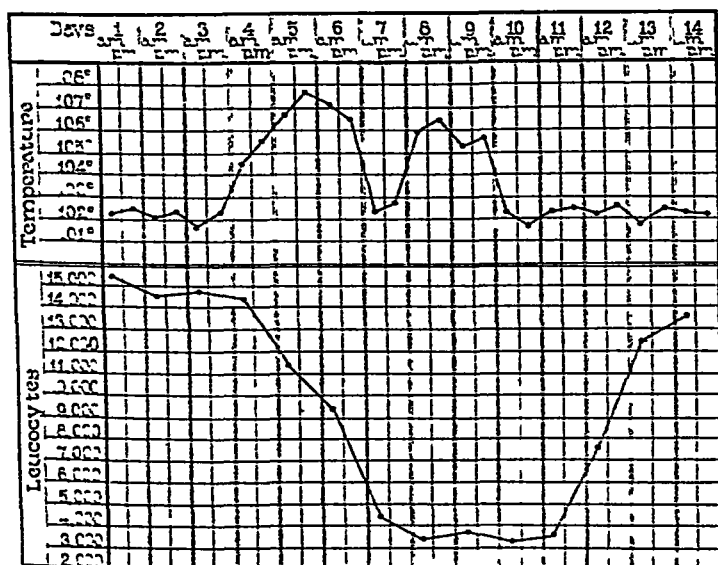


Fig 170.—Experimental dengue in the guinea-pig

animal produced the febrile and leukocytic reactions which we regard as experimental dengue fever.

**Animal Transmission.**—Blood obtained from dengue fever patients (preferably during the height of the disease) was inoculated into the guinea-pigs. This was employed both defibrinated and citrated and, in addition, a portion filtered through a Berkefeld filter. These inoculations were accompanied by specific febrile and leukopenic reactions in a varying percentage of instances. Of 142 animals used for the initial inoculation

of blood obtained from 16 human cases, 42 animals, representing 11 human cases, reacted characteristically. The reaction usually occurred on the third day, with a range of from two to five days as the limit.

The reactions were clear cut, consisting of definite febrile response and distinct diminution in the circulating leukocytes (see charts). The average leukocytic count ranges from 12,000 to 15,000, although higher and lower counts in normal animals may be found. The febrile rise produced was usually 105° F and higher. The leukocytic count was generally decreased by 4000 or 5000. The highest temperature recorded was 107° F and the lowest leukocytic count was 2000. The febrile chart often demonstrated the saddle-back curve as presented at times in the human dengue case. No evidences of rash or mucous membrane hemorrhages were noted in the experimental disease. While many strains of virus obtained from certain of the human cases could only be maintained through but few generations in the guinea-pig, others were propagated through twenty or more, and in one instance, fifty-two generations.

**Pathology**—Regarding the human pathology of dengue fever very little can be said for the reason the disease has afforded too few fatalities. Where death resulted from dengue fever no pathologic study accompanies the report as far as we have been able to glean from the literature. In the epidemic studies by us we did not hear of a single fatality that could be attributed to the disease. Undoubtedly the specific morbid process is responsible for mortality where the infection occurs in persons already suffering with some chronic or constitutional ailment or where those attacked are the extremes in age, that is, the very young and very old. However, even in these reported instances of mortality there is no specific mention of the pathology. The gross pathology occurring in the living case has already been mentioned, such as eruption, upper respiratory mucous membrane inflammation, jaundice, arthritis, hemorrhages, lymph-glands, and splenic enlargements.

In the experimentally induced infection of the guinea-pigs by the inoculation of dengue virus there occurs a rather constant

and characteristic gross alteration of the lymphoid tissues and of the spleen especially, which organ often attains a size three to four times that of the normal. The adrenal glands are also usually enlarged. These gross changes form a fairly constant pathologic anatomy.

The striking histopathology in the experimental animal consists of an endothelial proliferation occurring chiefly in the lymphoid tissues. There are also degenerative lesions of the parenchymal elements for the internal organs, especially marked in the heart, liver, spleen, and kidneys.

**Conclusions**—In conclusion it may be said that the causal excitant of dengue fever has been definitely proved to be filtrable, and to be present in the circulating blood of patients suffering with the disease. The specific virus is found in the blood on the first day of illness and as late as the febrile reaction persists. Furthermore, it has been established that the disease is not transmitted by direct contact with the sick person or the fomites, but through the bite of the mosquito which previously has fed upon dengue blood. It is not proved which species of mosquito acts as the carrier, though the weight of evidence is in favor of the *Aedes ægypti* or *Stegomyia fasciata*. It is also problematic whether the mosquito is a definitive host or simply a mechanical conveyor of the virus of dengue. There is very little experimental evidence in support of the view that the virus has a complete cycle and requires two hosts in order to complete its development.

While the exact nature of the causal excitant has not been finally determined, it is generally conceded that it is not a spirochetal form of parasite. Dark-field and special tinctorial studies of the dengue material—human, experimental, and cultural—have failed in our hands to reveal any visible spiral organism. We have succeeded, however, in propagating in the lower animal (guinea-pig) and in cultivating *in vitro* under anaerobic conditions minute spheric bodies. These globoid bodies were cultured from the blood of human cases and the blood of guinea-pigs in which dengue fever was experimentally induced. Growth colonization of these coccoids occur in special semisolid media.

Stained preparations obtained from cultures appear as minute globoids which are arranged singly, in pairs, and in short chains. Here it should be mentioned that in studying the morphology and cultural characteristics of these "bodies" which we believe to be living micro-organisms, we have fully appreciated the confusion that might arise from the presence of inert particles sometimes seen in highly specialized protein media. The morphology and pseudocolonization of such inanimate precipitates or crystallates are not, in our opinion, the minute organism herein described. The micro-organism readily passes through the Berkefeld filter that holds back a control culture of *Bacillus pyocyaneus*. The filtrate gives rise to a characteristic reaction in the injected guinea-pig, from which animal there can be obtained in pure culture the same globoid bodies as were used for inoculation. In the guinea-pigs the response to culture injection is comparable to that occurring in the human case, and that induced by the injection of human dengue blood into this animal. Therefore we are of the opinion that this cultivatable globoidal micro-organism is of etiologic relationship to dengue fever.

The authors have further demonstrated that dengue may be directly induced in the guinea-pig with fresh human dengue blood and that the specific virus may be propagated through indeterminate generations in this species of animal. The experimental infection closely resembles dengue in the human, differing only in the absence of exanthem. The primary fever follows regularly a definite incubation period of two to five days, and after a twelve-hour or longer intermission of the pyrexia there occurs a secondary rise in temperature which together with concomitant leukopenia presents in the experimental animal a syndrome identical with that of the human disease.

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# CLINIC OF DR. ALLAN EUSTIS

## CHARITY HOSPITAL

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### TYPHOID CHOLECYSTITIS

THIS young woman has been ill for the past month and is now convalescent after a rather stormy period. I wish to call your attention to her well-nourished condition, and her clean moist tongue, although she has had fever ranging from 100° to 105° F during this entire time. Her illness started April 10, 1925, with nausea, vomiting, headache, and pain in the back, located over the right lower lung. She was admitted to the service of Dr. Maes with a diagnosis of acute cholecystitis, and operation for same was contemplated. However, a total white count showed only 3250 white blood-cells and her blood agglutinated a culture of typhoid bacilli in dilutions 1 40 and 1 80, with moderate agglutination in dilution 1 160. Blood-culture showed Gram-negative, short bacilli, morphologically and culturally *Bacillus typhosus*. I first saw her April 20th, ten days after onset of illness, when her principal complaints were nausea, vomiting, and pain in the right side of abdomen in region of gall-bladder.

She presented the picture of a highly toxic patient, with dry, coated tongue, tympanites, temperature 104.5° F, pulse 100, and respiration 22.

Examination of chest was negative, as was also that of the nervous system.

The abdomen was quite tympanitic and the spleen could not be palpated. Palpation of the region of the right flank was acutely sensitive, and it was impossible to differentiate between kidney or gall-bladder as the site of pain. The urine showed a specific gravity of 1025, acid reaction, albumin present, great excess of indican, but negative for urobilinogen, bile-pigments,



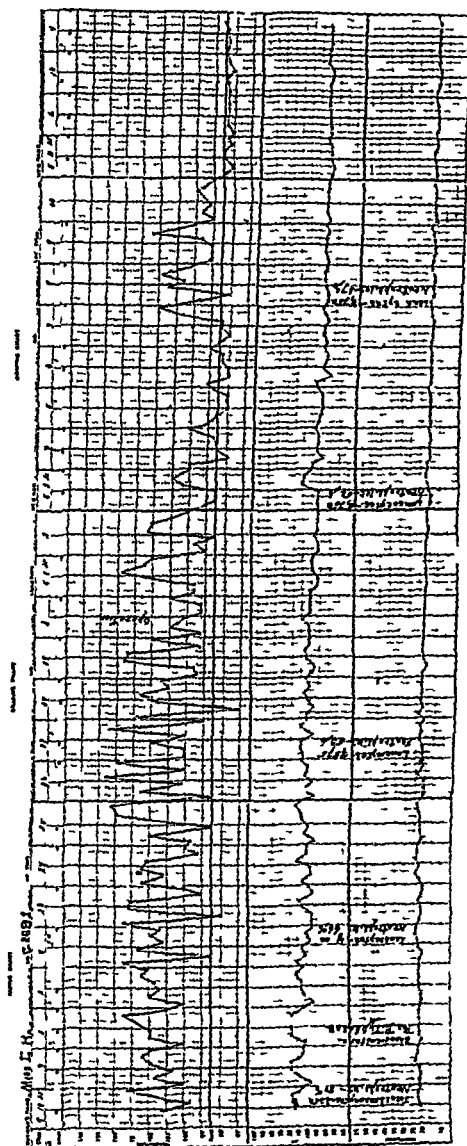


Fig 171

acetone, and sugar Microscopic examination revealed the presence of many hyaline, granular and finely granular casts, and many pus-cells

She was given a purgative enema consisting of Epsom salts 1 ounce, tincture of asafetida 1 ounce, glycerin 6 ounces, and soap-suds 1 pint, which was very effective in reducing the tympanites, when the edge of the spleen could be palpated extending on deep inspiration about 3 cm below the costal margin. Continuous proctoclysis of  $2\frac{1}{2}$  per cent glucose was started.

Dr Walther catheterized both ureters and reported as follows "Mild bacterium of both kidneys, organisms resembling typhoid bacilli." Both kidneys were lavaged with 3 c c of 0.5 per cent silver nitrate solution, following which temperature dropped to  $97^{\circ}$  F, but in a few hours rose to  $102.5^{\circ}$  F. Two days following (April 30th), on account of the constant nausea, pain in region of gall-bladder, and the sudden appearance of a strong reaction for urobilinogen in the urine, it was decided to drain the gall-bladder. Under ethylene and oxygen anesthesia, Dr Maes made a right rectus incision. "Exploration of kidney fossa revealed nothing. Liver very large and very red. Gall-bladder small, contracted, and thick walled. Aspirating needle revealed bile containing flakes of mucus. Gall-bladder drained with a Pezzar catheter. Usual closure of abdomen." Culture of bile was sterile after forty-eight hours.

Nausea subsided almost immediately after recovery from anesthetic, and she was able to take fluids by mouth in the following twenty-four hours, while in forty-eight hours she was able to take and retain cereals, toast, and thick soups. Her temperature has persisted, but at a much lower level and of an intermittent type for the past week, and she is now on the road to recovery because she is able to eat and retain sufficient nourishment not only to maintain her body tissues, but to replace that which was burned up during her period of partial starvation.

**Discussion of Case**—This case presents many interesting features.

First, the onset was more sudden than the usual typhoid case, second, the symptoms were those of acute cholecystitis, and third, the albuminuria, with pus and casts in the urine, and pain in the region of the right kidney suggested the possibility of pyelonephritis. The diagnosis of typhoid fever was first

suggested by the low white cell count, and confirmed by positive agglutination tests and blood-cultures. The failure to obtain a culture from the bile withdrawn from the gall-bladder does not negative the diagnosis of typhoid cholecystitis, as this has been the case in other instances reported by Lothrop and others, although some observers have reported positive cultures from the bile.

Few cases of typhoid cholecystitis have come to operation during the acute stage, as most of them have been treated medically, but, where there is sufficient nausea and reflex vomiting to interfere with proper nourishment of the patient, the indications for surgical drainage are self-apparent.

In typhoid fever the diet is the all-important factor, and a few remarks regarding same may not be amiss.

Before discussing the diet it may be well to consider the pathology of typhoid fever. As you know, it is a bacteriemia and the elevation in temperature is due to the liberation in the blood-stream of certain endotoxins liberated from the bodies of the typhoid bacilli after they are killed by the several defences of the body. In other words, the presence of fever denotes the circulation of a specific toxin, and when there is no more toxin circulating the temperature recedes to normal. All efforts should be directed toward limiting the toxemia to the specific toxin of the disease. Mallory many years ago showed that the toxin of typhoid bacilli is specific in that it stimulates proliferation of endothelial cells not only in Peyer's patches of the ileum and solitary follicles of the cecum and ascending colon, but also in the spleen, bone-marrow, mesenteric glands, and liver. In typhoid fever, therefore, we have a patient with anatomic lesions predisposing to stasis in that portion of the gastro-intestinal canal at which most rapid absorption takes place, and with a liver more or less deficient in its normal function. It is rational to assume that if toxic substances are formed in the intestines of the typhoid patient their effect will be more marked than in the normal individual.

My first impressions as to the influence of intestinal toxemia on typhoid fever patients were gained during my early medical

career, as a rural practitioner, in the years 1907-1911 On account of my earlier association with Prof. Chittenden, I combated any tendency to intestinal toxemia in all cases coming under my care, and I was impressed by the mildness of the symptoms in my typhoid cases as compared with those I had observed as an intern, in which milk every two hours was the standing diet

Warren Coleman has probably been most instrumental in forcing the profession to a realization that the average typhoid fever patient in the past was starved, and his work with Dubois on the metabolism of the typhoid fever patient has placed the feeding of the typhoid patient on a scientific basis These observers showed that the average typhoid fever patient requires or, 39.5 roughly, 40 calories per kilo of body weight per day to maintain weight equilibrium and spare tissue combustion A patient, therefore, weighing 60 kilos (132 pounds) will require 2400 calories per day in the form of food to replace the energy lost by radiation of heat alone Coleman (Jour Amer Med Assoc, September 12, 1914, 63, 932-935) stated as early as 1914, "The body utilizes carbohydrate in preference to fat and protein to meet the increased demand for energy in typhoid fever, just as it does in health when called on to perform additional work Consequently, carbohydrate should occupy a prominent place in the diet "

An analysis of many typhoid fever diets in use in some of our largest hospitals shows an utter disregard for the fundamental physiologic principles underlying the science of nutrition The first of these principles is that the need for protein in the diet above the basic needs for normal tissue metabolism is in direct ratio to the amount of muscular energy expended Second, that protein taken above the normal needs of the body exerts its specific, dynamic action in increasing combustion or metabolism Third, that the lumen of the gastro-intestinal canal is outside the body, and that food ingested is of no physiologic use until it has been digested and absorbed

I wish to impress upon you the fact that most printed typhoid diets contain much more protein and fat than is needed, or can

be handled by the gastro-intestinal canal. While the ingestion of excess fat has not been demonstrated as particularly harmful in the presence of sufficient carbohydrate, the same cannot be said for protein. I am well aware that many of our foremost clinicians deny the existence of such a thing as intestinal toxemia, and claim that the presence of an excessive amount of indican in the urine has little, if any, significance clinically. But, when one sees a dry, coated tongue, stupor and tympanites disappear with the elimination of indican from the urine, in case after case extending over a period of nearly twenty years, even though the patient may be ingesting far less than his calorie requirements, one is compelled to consider the probable causative factor of some toxins of intestinal origin.

It is well to recall the experiments of Vaughan some years ago, in which he was able to duplicate in experimental animals typical typhoid fever temperature curves by the injection of split products obtained by the hydrolytic cleavage of pure proteins. Coleman recognizes the influence of putrefactive substances from the intestinal canal and advocates a high carbohydrate diet with the idea of transforming the flora of the intestinal canal from the putrefactive to the acidophilic type, which was shown many years ago by Distaszo could be easily accomplished by diet alone.

My plan of dieting a typhoid fever patient, if seen early in the disease, before there has been much loss of body protein, is to keep the daily intake of protein at approximately 0.5 gm per kilo of body weight, given in such form as buttermilk, clabber, yolks of eggs, and sweet milk if the patient is free from indican, this latter being considered an index of protein putrefaction. If there has already been considerable body waste, the daily allowance of protein is increased to 1 gm per kilo. Fat is given to the point of complete digestion, the stools being watched for evidence of same, while carbohydrates are forced to the limit in the form of cereals, toast, crackers, vanilla wafers and sugar of milk, mashed potatoes, rice, fine hominy, and corn bread.

I have experienced best results by feeding patients three

times daily, giving them full meals, and between meals allowing nothing which requires digestion. This does not prevent the administration between meals of fruit juices or sherbets containing sugar of milk, which add to the caloric intake, but entail little or no work on the stomach. It is impossible to feed a patient such a diet if he is highly toxic, with a dry, coated tongue, and in such an individual, before any animal protein is allowed, he is kept often for two days on fruit juices with an abundance of fluids, and given frequent saline flushes. Peppermint candy sucked at frequent intervals will clean a tongue more readily than the most efficient nurse with an antiseptic solution. I accidentally discovered this during my rural practice, and since then have often used this simple method, thereby getting in carbohydrates, and at the same time cleaning the tongue and increasing the desire for fluids.

I do not wish to be understood as proclaiming that such a procedure is easy to carry out after a patient has already been starved, and whose tissues are desiccated. However, I do not recall during the past eighteen years a single case of typhoid fever under my care who, if fed early in the disease on such a diet with constant attention given to overcoming intestinal putrefaction, provided the patient has first been detoxicated before attempting to feed him, who has not enjoyed his meals, slept well, become free from most of the nervous symptoms usually associated with typhoid fever, and at the same time having a clean, moist tongue, with freedom from tympanites and diarrhea.

I have taught for several years that the dry, coated tongue and tympanites included in text-books as symptoms of typhoid fever are not symptoms of this disease, but are symptoms of improper feeding of the typhoid fever patient.

In this case under discussion the tongue became clean in forty-eight hours, while the tympanites disappeared in twenty-four hours and did not recur.

**Summary.**—1 Acute cholecystitis may complicate and be the predominating factor, as far as symptoms are concerned, in typhoid fever.

2 If it is of such severity as to interfere with the proper feeding of the typhoid patient, the gall-bladder should be drained surgically

3 In the feeding of typhoid fever patients carbohydrates should be the principal food-stuff, while constant attention should be paid to the prevention of intestinal putrefaction

# CLINIC OF DR J BIRNEY GUTHRIE

## CHARITY HOSPITAL

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### DOSAGE OF INSULIN AND TABLE FOR ITS USE INSULIN ON DAY OF WEEKLY FAST. CELL RE-EDUCATION TO OVERCOME INSULIN SHOCK ACCOMPANYING HIGH BLOOD-SUGAR

THE literature on the subject of insulin has become most extensive, and writers are entirely agreed as to its value in the treatment of diabetes. There are, however, some problems which still obtrude themselves as regards the methods of its use. We find, for example, a considerable divergence of opinion respecting the question of dosage, and in this discussion we shall be largely concerned with analyzing the question from this point of view.

During the last two years in the Charity Hospital and Touro Infirmary of New Orleans, La., I have had the opportunity of observing a large group of diabetics. These, together with a considerable group of private patients, furnished the material on which these remarks are based.

The question of dosage seems to be a most weighty one. Bound up as it is with the question of ultimate blood-sugar level, this latter question is a most important one to be determined.

It is rather startling to read from the hand of clinicians of note that they are content with reaching a blood-sugar level of 196 mg. For example, in a recent communication Ralph H. Major and Robert C. Davis<sup>1</sup> give a list of patients in whom blood-sugar levels of 345, 350, 225, and 196 respectively, because of insulin shock, marked the end of their attempt at further re-



duction. They say, "On several occasions an attempt was made 1, 2, 5, and 6 to lower the blood-sugar by increasing the dose of insulin, with the result that they had a mild insulin shock. In treating these patients the high blood-sugar values have been ignored and diet and dosage of insulin have been based entirely on urinary findings. Such management has proved satisfactory, although several of the patients worry when their blood-sugar is elevated, though they have no sugar in the urine."

In conclusion they say "We have learned from the study of these patients that the estimations of the urinary sugar have been a safer guide to therapy in this group of patients than the blood-sugar determinations." We see that in all of the cases of Major and Davis mentioned in the paper quoted, they were content to maintain their patients in a frankly diabetic condition apparently through the fear of a moderate insulin reaction. It cannot be denied that a patient who is sugar free, so far as the urine is concerned, is more comfortable than one who is excreting sugar. Yet can it be maintained that we are doing our duty by such a group of patients, unless we make a systematic effort to lower the blood-sugar level to something like normal?

I have had this same difficulty, and earlier in my experience suffered from the same fear of the moderate reaction as Major and Davis describe. We know that a certain improvement comes to the diabetic patient from even a moderate reduction of the blood-sugar level. Most encouraging is the disappearance of glycosuria and the relief from polyuria and itching. I have had a considerable number of cases where I have been able to bring about a reduction in blood-sugar from increased dosage of insulin, which seemed hopeless at first on account of reaction. Table 2, which shows the level of a group of cases at which maintenance conditions were maintained, would seem to bear out this conclusion. I have never encountered blood-sugars at the level described by Major and Davis, which could not be brought down considerably lower than their final maintenance figure.

In the literature of insulin, I have encountered only two statements as regards the dosage of insulin in its relationship to blood-

sugar Ira B Bartle,<sup>2</sup> in a paper entitled, A Surgical Use for Insulin, mentions a dosage of insulin determined about as follows "2 drops of insulin (U-20) was given daily for every 10 mg of blood-sugar in excess of 90 per 100 c c" Campbell and Macleod,<sup>3</sup> in their most extensive article on insulin, have this statement "It becomes necessary to add 2 units of insulin to the daily dose for each 0.1 per cent. if it is desired to lower the blood-sugar"

These two statements were evidently the result of clinical experience on the part of the writers. The safety of the procedure could only be determined by applying the dosage mentioned in a considerable number of cases and noting the result. We believed that the higher coefficient of the two was more nearly correct, and this translated into units is 2.5. In order to apply this readily in the clinic to the ordering of daily dosage of insulin, with the help of Dr M. A. Young, of the Intern Staff of Touro Infirmary, I constructed a table based upon a differential of 2.5 units of insulin per 100 c c in excess of 90. The table is given on page 946.

In order to determine the safety of this method of controlling the dosage we tabulated 31 cases now under treatment which have reached maintenance condition, and compared the final dose of insulin with that which was computed in advance from Table 1. In the 31 cases the average final dose is 47.7 units, and the average computed dose by the table is 34.6 units.

Of the 31 cases, 19 required a larger dose than that computed, 7 required a reduction, and 5 required no alteration whatever after the beginning of treatment. Judging by our experience in these patients, we are within safe limits in using the coefficient 2.5 as the basis for our table of computation. All of these cases were treated as ambulant cases, and no serious reaction occurred. We see more often the necessity for raising the dose rather than for diminishing it. Our averages of dosage seems to be about 33 per cent. too small, and we are tempted to increase the coefficient to, say, 3 units. However, I should feel much more secure in recommending the lower coefficient, namely, 2.5.

TABLE 1  
FOR DETERMINING DAILY DOSAGE OF INSULIN

Blood-sugar, mg	Units, insulin	Blood-sugar, mg	Units, insulin
100	2 5	295	51 25
105	3 75	300	52 5
110	5 0	305	53 75
115	6 25	310	55 0
120	7 5	315	56 25
125	8 75	320	57 5
130	10 0	325	58 75
135	11 25	330	60 0
140	12 5	335	61 25
145	13 75	340	62 5
150	15 0	345	63 75
155	16 25	350	65 0
160	17 5	355	66 25
165	18 75	360	67 5
170	20 0	365	68 75
175	21 25	370	70 0
180	22 5	375	71 25
185	23 75	380	72 5
190	25 0	385	73 75
195	26 25	390	75 0
200	27 50	395	76 25
205	28 75	400	77 50
210	30 0		
215	31 25		
220	32 5		
225	33 75		
230	35 0		
235	36 25		
240	37 5		
245	38 75		
250	40 0		
255	41 25		
260	42 5		
265	43 75		
270	45 0		
275	46 25		
280	47 5		
285	48 75		
290	50 0		

Reduction	
Blood-sugar, mg	Units insulin
85	—1 25
80	—2 5
75	—3 75
70	—5 0
65	—6 25
60	—7 5
55	—8 75
50	—10 0
45	—11 25
40	—12 5

The above table is based on an allowance of 2.5 units of insulin for every 10 mg per 100 c.c. of blood-sugar in excess of 90 mg per 100 c.c.

TABLE 2

No	Name	Color	Sex	Age	Initial blood-sugar, mg	Blood-sugar after insulin, mg	Estimated insulin need units	Insulin dosage, final units.
1	C. C. L.	C.	M	50	266	110	44	48 +
2	Mr. L. H.	W	M	42	170	100	20	40 +
3	Mrs. M. A. R. H.	W	F	59	306	133	54	48 -
4	Mrs. L. S.	W	F	46	266	105	44	92 +
5	E. L.	C	F	23	234	117	36	105 +
6	Mrs. E. L.	W	F	67	160	105	17 5	26 +
7	M. P.	C	F	24	143	91	13	13 0
8	S. G.	W	M	35	181	100	22	22 0
9	Mrs. N. D.	W	F	50	258	110	42	46 0
10	Mrs. M. S.	W	F	55	215	95	31	48 +
11	Mrs. M. J.	W	F	39	234	110	36	20 -
12	Rev. O. S.	W	M	48	266	80	44	16 -
13	Mrs. B. H.	W	F	35	190	95	25	30 -
14	James G.	C	F	49	332	117	50 5	60 +
15	C. H.	C	F	21	320	86	57 5	64 +
16	I. W.	C	F	44	250	91	40	30 -
17	A. W.	C	M	54	210	117	30	82 +
18	C. L.	C	F	39	166	117	19	25 +
19	M. P.	C	F	45	400	92	77	64 -
20	Mrs. M. S.	W	F	64	136	95	12	28 +
21	J. H.	W	M	55	200	125	27	54 0
22	R. D.	C	F	58	306	100	54	65 +
23	F. W.	C	M	47	160	100	17 5	38 +
24	Mrs. K. C.	W	F	58	286	125	49	55 +
25	Mrs. O. R.	W	F	50	242	86	38	40 +
26	I. J.	C	F	37	285	100	49	33 -
27	Mrs. C. S.	C	F	43	220	105	32	40 +
28	E. W.	C	F	48	190	126	25	47 +
29	J. D.	W	M	47	220	96	32 5	34 0
30	Mrs. M. H.	W	F	60	166	137	19	100 +
31	S. B.	C	F	44	195	86	26	79 +
					Average 204 3	Average 104 9	Average 34 6	Average 47 7

The sign (+) indicates that an increase of dosage above that originally computed from the table was eventually necessary.

The sign (-) indicates that dosage originally computed required reduction as the case progressed.

The sign (0) indicates that the dosage originally computed from the table was exactly suited to bring the patient's blood-sugar to approximately 100 mg. per 100 c.c.

Total white 17 (54.8 per cent) Total male 7 (22.6 per cent)

Total colored 14 (45.1 per cent) Total female 24 (77.3 per cent)

Our records today are in marked contrast to those of a year ago before we began this method of insulin computation.

In using the table on page 946 it is assumed that a daily diet identical in glucose equivalent will be maintained.

At the time of each blood-sugar determination the table may be used. If the normal blood-sugar level has not been reached, a new daily insulin usage may be thereby easily determined before the next period.

If the blood sugar reaches normal the dose of insulin is maintained in the absence of severe reactions. Severity of reactions call for additions of carbohydrate in the form of orange juice in gradually diminishing daily quantity until patient has become reaccustomed to lowered blood-sugar level. This new level can with patience usually be reached and established.

In the event of reaching a hypoglycemic level, the table indicates the necessary reduction of insulin.

Formerly, it often required weeks to arrive at the ultimate dosage to be given to a patient. It was much more an affair of trial and error than it is at the present time by following this method. The dose so determined, at the start, seems enormous, but, as we have seen, in the majority of cases a further addition is necessary. Let it not be understood that one can fix on a dosage which shall be sufficient for the entire treatment. Too many factors operate to make this possible.

It can hardly be denied that one of the greatest benefits that comes to a diabetic under treatment is the relief of the insular cells of the pancreas from the overstimulation of continued hyperglycemia. It would seem to be correct, in theory, that it is most desirable to bring about this "insular rest" at the earliest possible moment. Also it seems correct to establish the *optimal* dietetic conditions for the patient while the relief is in process of accomplishment. By this *optimal* diet we mean, of course, a diet which furnishes the necessary quota of energy, protein, and essential vitamins.

One can easily infer that if such a system of treatment were proved to be correct, it would follow as a corollary that the treatment of diabetes would necessarily be best limited to those who have at hand the facilities of making blood-sugar determination. I believe that much of the confusion that exists today comes from a rather commendable desire on the part of some of us who have been teaching this subject to find a method which should enable the doctor who does not possess these facilities to treat the disease. At the present time I believe that the treatment of diabetes should be in the hands of those who can properly control the case by blood-sugar determinations. The technic of these determinations has been made easy for anyone who has had a moderate amount of laboratory training. I do not believe that any student should be allowed to graduate in medicine who has not had such training. The situation is identical with certain surgical operative procedures, the performance of which is not within the scope of the average practitioner. Lest I be misunderstood, I should say that in my opinion occasional blood-sugar determinations are indispensable, and

I believe that he who cannot command them should delegate the treatment of his cases, or at least have them checked occasionally by a competent laboratory

CASE I—C C L. This patient is a colored man aged fifty-one. He is a minister and of more than the average intelligence for his race. Five years ago he weighed 245 pounds, height, 6 feet. Since this time there has been a gradual loss of weight. On admission to the Diabetic Clinic of Touro Infirmary November 2, 1923 he weighed 200 pounds and was suffering with neuritic pains in legs and general muscular weakness. Polyuria was troublesome and the patient complained of "nervousness." The apex of the heart is found in the sixth intercostal space displaced 2 cm. outside the midsternal line. A soft systolic murmur is heard. No edema or dyspnea is found. This man when first seen had a fasting blood-sugar of 400 mg. per 100 c.c., and on a diet composed of C 51, P 56, and F 125 he was excreting 35 gm. of sugar in twenty-four hours. After one month of simple dietary restriction he had lost 11 pounds in weight and his blood-sugar was reduced to 200 mg. on a diet of C 31, P 29, F 69 (861 calories). On this diet he did moderate work, excreting a trace of sugar. The diet was obviously inadequate and a clear indication for insulin existed. At the time we lacked the experience we now have in ordering at once the insulin that the patient would probably need. In this case only 8 units were given at first. A gradual increase in the dose was carried out until it finally reached 44 units, the present dose. Now he receives a diet of C 40, P 45, F 24 (1544 calories) with a glucose equivalent of 77 gm. This diet is ample for his needs in point of energy value and protein content. All of his symptoms have disappeared and his weight (178 pounds) has been stationary for eight months.

Our treatment in addition to the carbohydrate adjustment has been one of undernutrition and weight reduction up to eight months ago, since which time we have kept his weight stationary.

It might be suggested that a further weight reduction might enable us to use less insulin. We have tried the lower diet, and apparently he is better on this one. It is my own opinion that the fear of a large daily dose of insulin in a patient who needs it is today more or less unfounded. Eight months have gone by and this patient's regimen has been unaltered. There has never been in this period a single semblance of a hypoglycemic reaction from insulin. As experience increases, I find myself less and less afraid of Joslin's "stults."

This man uses a gram scale, weighs his food, calculates his diet, and tests his own urine, and administers his own insulin.

During his entire treatment we have used the weekly fast, and, since insulin treatment, 5 units of insulin increased to 6 units have been given on the fast day. During one period we gave him during alternate weeks the same quantity of food divided into six daily rations, with a day of fast, and the following week the same quantity in seven daily rations omitting the fast day. He was more content with the arrangement, including the fast day. No appreciable difference resulted in the blood-sugar during these two weeks of trial.

So far as I know, I am alone in using insulin during a weekly fast day. I have even used it to advantage, I believe, in more rapidly establishing resting conditions for the pancreas in a number of cases that are able to get along without it otherwise. I am still making observations along this line and may have something to report in the future.

The weekly fast throughout the course of this case was carried out. Just as soon as it was manifest that an adequate diet for the patient demanded the use of insulin, the weekly fast was continued, with the addition of a morning dose of 5 units of insulin. Here we were trying to intensify the effect of the fast with the insulin.

Not only were those days free from any semblance of reaction, but on one occasion when he showed a constant fasting blood-sugar of 124 mg and was accustomed to using 40 units of insulin daily, in error, the 40 units were taken on the day of the fast. No reaction of the slightest degree was noted on this day. Previously the patient had suffered reactions at 143 mg even on his usual diet, but, by *training*, these reactions had been overcome and he was quite comfortable on a new level of normal range.

I can recall nothing in the literature of the subject which attempts an explanation of the results I have repeatedly seen in the course of the re-education of the patient. He becomes, as a result, accustomed to this newly established level, and seldom fails to exhibit corresponding improvement of blood sugar. The word *training* suggests itself, adapted from W. S. Plummer's description of the transformation that occurs in the thyroid

gland in exophthalmic goiter when a pathologic secretion is replaced by a normal one, even though in abnormal quantity

I am convinced that cell training is what occurs in these cases. At all events the idea constitutes a working hypothesis which seems to satisfy the conditions

Cases 9 and 27 (Table 2) were conspicuous examples of a readjustment to new blood-sugar conditions. These patients reacted rather severely and constantly at first to the advent of a blood-sugar much above normal. Now they are easily kept within normal

I can testify that it took courage on the part of the patient and faith on the part of the doctor in the correctness of his idea to bring them where they now are

The case of this man is interesting from several standpoints. He unquestionably should be classed as of a moderately severe type. The initial blood-sugar before any restriction was exercised was 400 mg. There has never been a single hospital day. He has co-operated to the fullest. The blood-sugar is now at normal levels. He has been re-educated to this level. The threshold of sugar excretion is, as is the case with all the cases I am today presenting, high. An efficient control of such cases by means of urinary examinations alone is impossible

It is rather striking to note that, in this case, 6 units were given during a fast of eleven hours after a meal, and then hourly determinations of blood-sugar were made for three hours. A gradual rise occurred and a subsequent twenty-four-hour determination shows a slightly higher level than the previous morning. The rise after insulin (subcutaneous) was unexpected and suggests a mobilization of glucose greater than normal. This is probably an insulin effect on the liver

TABLE 3 C C L

Showing behavior of blood-sugar (in mg) at intervals of			
one hour,	two hours,	three hours,	thirty-seven hours, resp
B S	B S	B S	B S
105 mg	108 mg	115 mg	107 mg
Effect of 6 units of insulin given July 25, 1925, one hour before first observation			



We were so struck by the rise in blood-sugar that occurred in this case during the fast day that with the help of Drs J M Donald and M J Duffy, my interns at the time, we undertook to carry on somewhat the same procedure in 4 cases in the ward at the time. All of them were well along in treatment, all moderately severe cases.

August 24, 1925 The blood was taken fourteen hours after the last meal. Results are shown below.

TABLE 4

Shows blood-sugar in mg per 100 c.c. at varying intervals following the giving of 6 units of insulin given to 4 patients and after a fourteen-hour fast. Insulin given in all cases subcutaneously at 7:30 A. M., August 24, 1925.

Name		½ hr	1½ hrs.	2½ hrs.	3¾ hrs.	4¾ hrs.	37½ hrs.
L L	*	137	91	110	86	93	100
M T	160	148	124	108	95	95	124
H T	105	100	66	71	76	91	86
M W	105	105	93	83	83	80	95

\* No observations, blood clotted.

No reaction occurred in any of the 4 cases as the result of the insulin experiment in the fasting condition.

It will be seen from the above that the behavior of all 4 of these patients to insulin during a fast is distinctly different from that of C C L as regards blood-sugar levels.

**CASE II—E L.** This young colored woman, aged twenty-four years, is a graduate nurse, and for some time previous to her admission to my service, November 4, 1924, to Charity Hospital, was employed in an institution in Louisiana. The following history was obtained:

Sugar had been found in July, 1923, but under dietary restriction alone the urine became sugar free in December, 1923. She abandoned her dietary regimen from this time until January, 1924, when she found herself gradually becoming weaker, and when sugar again appeared in her urine. At this time her attending physician put her on 30 units of insulin and restricted her diet. On August 1, 1924 the dose was increased to 40 units daily, which she continued until August 15th. Her dietary restriction was continued and she felt quite well, working constantly, and on a "moderate diet restriction" until October 24, 1924, when she complained of a "pain in the throat," and at 10 P. M. was found in a coma. She is reported to have had a blood sugar at this time of 500 mg., and 20 units of insulin were given.

TABLE 5

October 25, 1924	E L	Day of first coma	
Time		Insulin units	Blood-sugar mg
9 A M		20	445
10 A M		20	440
11 A M		30	440
12 M		30	380
2 P M		30	334
4 P M		30	347
Total		160	

Fluids were given by proctoclysis and hypodermoclysis (presumably glucose solution)

October 26th Still in partial coma, B S 72 Remained in coma thirty-six hours

October 27th Patient clear, B S 73 Put on diet "30 units insulin" daily

October 28th Pain in left buttock

November 2d Deeply seated abscess of left buttock, evacuated

November 3d Restless Rapid and deep breathing

November 4th Admitted to Charity Hospital

The condition of this patient November 4th, at the time of her admission to Charity Hospital, was most serious. The breathing was of the typical Kussmaul type. She had been in coma for thirty-six hours, but could be roused for an instant. The breath reeked of acetone and the urine gave a marked reaction to acetone, and an intense copper reduction. The eyeballs were soft. She was emaciated, but physical examination showed no abnormality of note. During the forty-eight hours following no food of any kind was given. Fluids were administered in the shape of salt solution by mouth, hypodermoclysis, and proctoclysis, and, as may be seen in Table 6, a total of 280 units of insulin were given during the twenty-four hours following admission. The blood-sugar was reduced by this from 444 to 200. Four hours after this treatment was begun the patient was conscious and awake. No alkalies and no glucose were given at any time. Table 7 shows the diet and insulin given during the month of her stay. Her weakness was extreme and the general pains were such as to suggest a diffuse polyneuritis, but deep reflexes were never impaired. The mind was clear after consciousness returned, but the muscular weak-

ness was most notable. No attempt was made in this case to further reduce blood-sugar. We deemed the dose (80 units) to be all we dared to give, and contented ourselves with a blood-sugar level of 200 mg. Occasional reactions of mild degree deterred us from further increase.

December 10, 1924. This patient was admitted to the diabetic clinic under my care at Touro Infirmary, and keeping up practically the same dietary, 40—32—100, with insulin 80 units daily. During January, 1925 she suffered intensely with pains in legs, and in the latter part of the month developed a left circumflex neuritis, followed by a Zoster, marking very discretely the superficial distribution of the circumflex nerve. A few cases of this occurrence have been noted in the literature. It is of interest as it serves only to show that an active polyneuritis with this very typical manifestation in the circumflex region was existing with the patient sugar free (from standpoint of urine) and with a blood sugar of less than 200 mg. Amelioration was obtained by persisting in the insulin dosage and the prescribed diet, gradually diminishing the quantity of orange juice allowed when mild reactions occurred. We were thus able to get the blood-sugar down to 150 without reactions. The weight loss was considerable from pain and our usual quota of cod-liver oil, 10 c c three times daily, was given as part of the daily fat allowance. Patient improved and went back to work. She is at present giving herself the insulin and keeping up the diet.

We believe that by patient work it will be possible to further improve this patient by re-education to lower the critical level, so that a normal level can be established.

TABLE 6 E L

Second coma		Admitted November 4, 1924 to Ward 40A, Charity Hospital		
Date, 1924	Diet, C P F	Blood-sugar mg		Insulin units.
November, 1924				
4	Water only	444—11 A M		170
		286—3 30 P M		
5	Water only	190—8 A M		110
Total in twenty-four hours				280 units

It is not often that one is able to show, apparently in good health, a patient who has been through two episodes of diabetic coma. One can remember the thrill that the early insulin experiences brought in this regard. Here is a patient whose insular need is 80 units to enable her to live and work. The final insulin

TABLE 7 E L

Date, November, 1924	gm.	Diet, C. P. F., gm.	gm.	Blood-sugar mg	Insulin units.
6	34	15	30	200	140
7	51	29	65	156	140
8	61	32	66		100
9					80
10	67	32	66		80
11	61	32	100	215	80
12	70	32	100		90
13	66	32	100		75
14	61	32	100		75
18		32		240	75
29	40	32	100	240	80
December 4		32		190	80

Discharged December 4, 1924 from Charity Hospital

dose constitutes a most excellent numerical coefficient of the pancreatic deficiency. Certainly this is a much more definite expression of the severity of the disease than is the highest possible glucose equivalent of a diet without glycosuria. Measured by the standard insulin dosage we should certainly say this patient were a severe diabetic. She also has a high threshold (160 mg) and has to be judged by the blood-sugar and not by the occurrence of glycosuria. Her blood-sugar we have not been able to reduce below 143, because she was satisfied with her condition and went back to work. I am quite confident we could get her past the point of "reactions" if she would give us the opportunity. One complication which was of considerable interest occurred in the month of February. Pains in the legs and weakness occurred at this time. Pain in region of the left shoulder occurred and in the circumflex area. This was followed by a vesicular eruption in the same region—a typical *zoster circumflexus*. This has been the subject of special communication by one of the French authors.

It will be noted that this patient was not fed during coma. Indeed, there were two full days and an intervening night that fluids by mouth were given and hypodermoclysis (water and salt solution) and no carbohydrates. Also it is of note that no alkalies were used. Patient was conscious and awake four hours after treatment was started.

CASE III—M E Our next patient is also a colored woman. She is a laundress and her age is fifty-two. She was admitted to my service in Charity Hospital, September 28, 1923.

She gave a history of weakness and intense vulvar pruritus. The onset was apparently one year previous to admission. On admission the urine showed sugar, moderate reaction only, but the blood sugar was 266 mg per 100 cc. She was at once placed on a computed diet and given insulin in gradually increasing doses, beginning with 6 units daily. We were able to get her very promptly sugar free and discontinued her insulin. She was discharged from the hospital November 12, 1923, with blood sugar of 200, to be cared for in the diabetic clinic. She did not apply for admission to this clinic (Diabetic Clinic, Touro Infirmary) until March 13, 1924, when an acute respiratory infection occurred which caused her to suffer some general pains. She had been instructed in computing her diet while in Charity Hospital, and without any supervision had adhered to the diet prescribed from December 12, 1923 to March 13, 1924, with the result that her blood sugar had diminished from 200 to 153 when next seen. A few days of further restriction sufficient to bring the blood sugar down to an average fasting level of 133 on a diet composed of C 50, P 50, F 100. Further restriction (in calories) would cause too much of a weight loss, and was not carried out. A second course of insulin units (8 daily) was given with the diet unchanged, and under this blood sugar averaged 100. She was apparently just as well with blood-sugar 133 as at the lower levels and the insulin was discontinued once more.

This case is of interest because of the high threshold of sugar excretion, 250, because of the success in having her after two weeks' sojourn in the hospital sufficiently instructed to carry out her diet and make her own urinary tests away from all medical supervision.

The patient herself cannot read or write, but nevertheless she now administers insulin to herself and keeps her diet with the help of her granddaughter, a girl of fifteen, with a satisfactory degree of accuracy.

One is struck by the frequency with which one encounters a high threshold of sugar excretion in these cases. This factor makes necessary the periodic blood-sugar estimates of tolerance. Her status was as follows:

August 30, 1925

Diet C 31, P 42, F 61—calories 841

30 units of insulin Blood sugar 133

Comparing this with May 5, 1924, when we find a diet C 42, P 29, F 52—calories 752—glucose equivalent, 61 gm insulin, 5 units blood sugar, 110

Apparently a loss of tolerance of 150 per cent has occurred accompanied by a gain of weight of 152 to 158 pounds. This gain in the low diet causes doubt as to the validity of the figures obtained from the laboratory (B M R +18). At no time has there been given to this woman a diet equal to her theoretic daily caloric need (2010 calories). The maximal diet has been 1550 calories since the beginning of treatment, the average diet during the last six weeks, 1201 calories. It is most necessary just now to keep up her restriction and to combat the gain in weight. She is now taking 8 units of insulin daily.

A survey of a large series of diabetics convinces one of the necessity for keeping obesity foremost in mind in planning the management of the patients who are overweight.

You will notice that all 3 of the patients I have presented for your attention are of the colored race. You will notice also that in Table 2, taken from my Touro Clinic records by dates, it happens that 14 out of 31 of these cases are colored patients. In this clinic at large the colored patient predominates.

I have chosen these 3 colored ambulant cases to show to you and to my colleagues in the South how possible it is to secure the co-operation of the negro in carrying out dietary measures in diabetes. Living in the South, and as I thought, knowing the negro, I have been very much surprised at the results obtained in this regard. The dietitians have often commented to me on how much more readily the negro could be induced to take a diet composed as largely of 5 per cent vegetables than are the white patients. He is more used to this type of food.

I have adopted the plan of giving at the earliest possible time a diet which is comfortable to negro patients. By so doing I have avoided the large number of initial desertions which was my experience several years ago.

One can usually find someone in the family to supervise the dietary measures and to give the insulin, if such is necessary. I have a number of patients on a high dosage who, like M. E., cannot read or write. Some are less fortunate than she.

in having "education" members of their families to do this for them.

The diet cards of Joslin\* have been of enormous service to me in giving instruction to laymen and medical men regarding the ordering of diets. Even with the assistance of a skilled dietitian they have a very decided use in an out-patient clinic.

My thanks are due to Drs. Ben E. Nelken and S. B. McNair for material assistance.

In concluding, let me urge perseverance in bringing the patient to something approaching a normal blood-sugar level even in the face of mild reactions at first. If this is not done, we have surrendered ignominiously and have abandoned the patient to his disease, just as surely as was the case before insulin when compromise diets were the rule. Re-education of the patient must occur before success can come to us in diabetes. This re-education must include his entire being, physically and psychologically speaking, and must extend to the habits of his ultimate cell life.

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\* Form J 4, Thos. Groome & Co. Inc., 105 State St., Boston

# CLINIC OF DR I I LEMANN

## TOURO INFIRMARY

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### PITFALLS IN THE DIAGNOSIS OF DIABETIC COMA

- 1 Diabetic Coma Without Ketonuria
- 2 Coma, Non-diabetic, With Glycosuria and Hyperglycemia

THE diagnosis of diabetic coma should be, it would seem, relatively simple. There are, however, many pitfalls. In a patient known to have diabetes it is usually easy to recognize the signs of the oncoming coma. The characteristic hyperpnea, which may develop into the classical Kussmaul air-hunger, the drowsiness, the restlessness, the peculiar acetone odor to the breath are signals which point the way to the correct diagnosis. The finding of acetone, diacetic acid, and sugar in the urine establishes the diagnosis on a firm basis. Further refinements of laboratory investigation in recent years, such as the determination of the carbon dioxide tension of the alveolar air and the carbon dioxide combining power of the blood-plasma make it possible to estimate the impairment of the alkali reserve of the blood and hence to express the severity of the condition in almost mathematical terms. The difficulties in the diagnosis, therefore, lie not so much in this direction, namely, the recognition of the diabetic coma in a patient in whom we have had reason to watch for it and to fear it. Even here, however, some difficulties arise, for a known diabetic may become comatose, as Root<sup>1</sup> has shown, not because of his diabetes but because of some intercurrent condition, as, for example, septicemia, meningitis, cerebral hemorrhage, or an uremia. Root<sup>1</sup> reports one case of streptococcus meningitis in a known diabetic patient where the fact that the carbon dioxide combining power of the blood-plasma was forty-six volumes per cent. ruled diabetic coma out of the question and made it necessary to search for



another cause for the coma. There are two other factors which may well serve to confuse in the case of a person known to be diabetic. Both of these have arisen, as Root<sup>1</sup> points out, since the discovery of insulin. First, the coma of a diabetic patient may now be not a true diabetic coma but the coma of insulin overdosage. Second, diabetic patients will now live very much longer and more of them will reach the "uremic zone of old age." The differential diagnosis between insulin coma and diabetic coma will rest, of course, upon the examination of the urine for sugar and for ketone bodies, or, better still if possible, upon the determination of the blood-sugar level. There are usually many symptoms pointing to the insulin overdosage long before the coma occurs, nervousness, apprehension, abnormal hunger, profuse sweating, excitement, disorientation, and sometimes even mania. I have never seen insulin coma without some of these prodromal phenomena, but, of course, it is quite possible that such of them as a patient might have could occur while the patient was quite alone. He might, therefore, be found deep in his coma without any knowledge on the part of others of any previous symptoms. Such a patient is usually drenched with perspiration and the pupils are usually widely dilated. The diabetic coma patient, on the other hand, has usually a dry skin, even where the surface is cold, as it usually is in the later stages. The eyeballs are soft, the patient with insulin coma does not present this characteristic phenomenon. The differential diagnosis between uremic and diabetic coma in a known diabetic is even more difficult. I shall discuss this further when I relate to you one of the histories.

We may not even assume that a diabetic patient whose urine gives a Burgundy red color with ferric chlorid has diabetic coma, for this reaction may be produced, as you know, by salicylic acid or its derivatives. We must not fail, therefore, to test such a reaction still further by boiling, if the reaction is a true one for diacetic acid, the Burgundy red color disappears on boiling, if it is due to salicylic acid, the color remains.

It is unfortunately true that many cases of diabetes go undiagnosed before the onset of coma. It has been my fortune to

see a series of coma cases in whom the disease went unrecognized for many long months in spite of typical symptomatology. I recall the case of a young girl about thirteen in whom the air-hunger was so severe as to cause a "tirage" such as is seen in laryngeal diphtheria or other obstructions of the larynx. While she was in this condition she was seen by a physician whom she had never previously consulted and who was ignorant of the numerous warning signals of the disease which had been present for nearly a year. His first impression of her was that there must be some laryngeal obstruction, and it was only after a laryngoscopic examination had proved negative and after he had made a urine examination that the proper diagnosis was established.

Our greatest difficulty arises when we are confronted with fully established coma in patients whom we have never previously seen and concerning whom we can obtain only a fragmentary history—a misleading one, or even no history at all. I shall not attempt here to enter into a discussion of the differential diagnosis of the various causes of coma. An enumeration of them will suggest to a large extent the investigations which we must undertake in order to differentiate between them, trauma with concussion of the brain or fractured skull, morphin poisoning, cerebral hemorrhage, meningitis, and encephalitis.

I wish now to relate to you several cases which illustrate some unusual pitfalls.

Case I—Mrs. Z, No. 2021, age forty-four. Was seen June 19, 1923, about noon. She had been in profound coma since 7 o'clock of the preceding evening. The surface was hot, the cheeks flushed, she was markedly emaciated. The mouth was very dry, the tongue parched and red. Respirations were deep, 34 to the minute. Pulse was full and regular, 104. Pupils were moderately contracted and did not react to light. The eyeballs were soft. The heart and lungs were normal. The abdomen was flat. The liver and spleen were not felt. The urine gave a heavy reduction with Fehling's solution, but showed no acetone and no diacetic acid. The blood-sugar was 760 mg per 100 c.c. of blood at 10:30 A. M. She was given 50 units insulin (letin H-10) at 12:30 P. M. At 2:15 P. M. the blood-sugar had fallen to 532 mg per 100 c.c. of blood. 3:30 P. M. she was given 20 units of insulin intravenously. 5 P. M. the blood-sugar was 314 mg per 100 c.c. of blood. 7:30 P. M. 20 units of insulin subcutaneously. 10 P. M. blood sugar was 285 mg per 100 c.c. of

blood, 10 units of insulin subcutaneously June 20th, 3 30 A M 5 units of insulin subcutaneously 12 30 P M blood-sugar was 83 mg per 100 c.c. of blood The patient had begun by 7 P M of June 19th to complain when she was stuck with the needle, and by 11 P M she aroused when spoken to and extended her tongue when she was requested to do so By 8 A M, June 20th, she was wide awake and answered all questions It was possible subsequently to adjust her diet and her insulin so that she gained strength and weight as is usual with such cases *At no time did her urine show acetone or diacetic acid*, although there was subsequently a rise of the blood sugar to a level of 388 mg per 100 c.c., on the fourth day because of inadequate insulin dosage This patient did very well until November, 1924, when because of an acute infection and a gross violation of her diet she came again to the verge of a coma This time, however, she was merely somnolent with some hyperpnea The urine showed 2 per cent sugar, a strong acetone reaction, and a trace of diacetic acid The blood-sugar level on the second admission (November 19, 1924), was 592 mg per 100 c.c. of blood It was again quite easy to rescue her from the coma and she has subsequently done very well, gaining constantly in strength and weight She went from 81 pounds in July, 1923 to 112½ pounds in August, 1925 The urine had never shown any abnormality other than the sugar and at the time of the second admission acetone and slight diacetic acid The blood-pressure was 130 systolic and 78 diastolic

This patient finally died in coma during November, 1925 She had developed extensive edema in the month previous In the final coma there was no impairment of the alkali reserve of the blood The urine showed no sugar or any ketone bodies, although the blood-sugar level rose to 285 mg per 100 c.c. when uncontrolled by insulin Her blood-pressure was 196 systolic and 100 diastolic There was evidence suggestive of an intracranial hemorrhage, the face becoming asymmetric, the tongue being protruded to one side, and the leg and arm of that side becoming flaccid

**Summary.**—The diabetes of the patient, though characterized by a classical symptomatology, was not diagnosed until she was in diabetic coma No diacetic acid was ever present in her urine though no doubt exists in view of the history, the other findings, and the results of insulin treatment that the first two comas were purely diabetic Evidence of a coexisting nephritis was finally found

**Case II.**—Miss D, No 2374, age fifty-seven Was seen in consultation on May 29, 1924, about 9 P M She had gone into coma about 7 P M Her physician said that the patient had been in good health until 1919, when she had influenza and developed signs of heart failure She had, however, paid very little attention to her condition until 1923, when the swelling increased and she had, besides the edema of the legs, some fluid in the abdomen She was kept in bed ten weeks at this time Later she was able to go about to some extent, but the condition soon returned and she was again forced to

go to bed. She had been in bed some three or four months prior to May, 1924. For some time she had been passing great quantities of urine, but this fact had been attributed to the diuretic drugs which had been given. The edema and ascites had disappeared. In the past year she had lost 75 pounds. It was said that at the last urinalysis three weeks previous to her coma no sugar had been found. Sugar had been found in the urine for the first time on the morning of May 29, 1924. That afternoon she became very restless and dyspneic, for this her doctor ordered a tablet of dialacetin. The sleep that ensued was attributed to the dialacetin. The patient was a somewhat obese, prematurely old woman, with marked edema of the legs and insteps. She was profoundly unconscious. The skin was dry. The pupils were equal and moderately contracted and did not react to light. Patellar reflexes were not elicited. Plantar reflexes were normal. Mouth was open and the jaw fell back. This rendered the respiration difficult. Patient was hyperpneic, respirations being 42 per minute. The lungs were normal, the heart rapid, 135 per minute, but regular. There was no murmur and no accentuation of the second sound. Peripheral vessels were sclerosed. Blood-pressure was 160 systolic and 80 diastolic. Abdomen was flaccid. There was apparently no fluid present. Liver and spleen were not felt. Lumbar puncture showed fluid under moderate pressure. The first tube was tinged with red, but the other tubes were perfectly clear. The examination of the urine drawn by catheter was as follows: Specific gravity, 1030, acid, albumin, slight trace, sugar, 14, *diacetic acid negative*, many fine and coarsely granular casts. The blood-sugar was 621 mg per 100 c c of blood. This was at 9 40 P M. Fifty units of insulin were given intravenously. May 30, 1924, 1 A M, blood sugar was 494 mg per 100 c c of blood, 50 units of insulin intravenously. 8 A M patient still profoundly comatose. Temperature 103° F, 20 units of insulin had been given at 5 A M. Blood-sugar at 7 A M 286 mg per 100 c c of blood. Insulin 9 A M, 10 units, 1 P M, 10 units, 5 P M, 10 units, 5 15 P M, 30 units, 9 P M, 40 units, a total of 220 units in twenty-four hours. On May 31st she was given (in the second twenty-four hours) 68 units, and on June 1st 95 units, on June 2d 108 units. She had begun to show signs of returning consciousness already on May 30th. These were still greater on May 31st, but it was not until June 1st that she became well oriented. The small doses of insulin on the second day were due to the fact that the urine showed only faint traces of sugar and the large doses were postponed until the report on the blood-sugar came from the laboratory, for we feared to reduce the blood-sugar below the normal. Because of the absence of diacetic acid from the urine we were uncertain that we were dealing with diabetic coma. Uremic coma seemed more probable, in view of the history and the urinalysis. For these reasons our insulin therapy was for a while less bold than it should have been. The urine was always negative for diacetic acid and showed acetone only on the first examination. The patient subsequently developed some superficial gangrene of the toes, which finally healed without loss of tissue. She also had a phlegmon of the upper right arm, which went on to pus formation and had to be opened under local anesthetic. Electrocardiogram showed auricular fibrillation. There was unusual difficulty in adjusting doses of insulin, and at one time it became necessary

to rescue her from an insulin coma which came on quite suddenly with only a few premonitory symptoms. She was finally discharged on June 24, 1924, with a diet of carbohydrate 70, protein 50, fat 120, insulin 20 units before breakfast, 10 units before lunch, and 10 units before dinner. Subsequently, at home she was fairly comfortable until finally the evidences of cardiac failure increased, and she died April 9, 1925 not in coma.

*Summary*—A patient with advanced heart and kidney trouble developed coma. Her diabetes had not hitherto been recognized. In spite of high blood-sugar levels she had relatively low grade of glycosuria and no ketonuria. She was rescued from coma by the usual insulin therapy. The absence of ketonuria was attributed to impaired kidney function.

Both Cases I and II illustrate the fact that we may have fully developed diabetic coma without the presence of ketonuria. Unfortunately, in neither of these cases was the grade of ketonemia ascertained. It seems quite probable that in both cases the failure of the ketone bodies to appear in the urine was due to the nephritis and the inability of the kidney to permit these bodies to pass through. This may not, however, represent the complete explanation. A number of cases of diabetes mellitus with apparently severe acidosis, but without the presence of acetone bodies in the urine have been reported in the literature. Starr and Fitz<sup>2</sup> refer to seven such reports and several more have appeared since their publication. Starr and Fitz studied the urines of a series of diabetic patients to determine whether organic acids other than the ketones are ever excreted in any significant amounts. They believed that the data they obtained suggested the occurrence in diabetic acidosis of organic acids other than the acetone bodies and that these organic acids played a part in the production of the symptoms. They considered that the group of cases in which there was reason to believe these unknown organic acids were the factor producing acidosis require "alkali as urgently if not more urgently than they require insulin, since insulin will clear up the acetone body acidosis, but may not affect the acidosis due to other acids, and the alkali released by the disappearance of acetone from the blood and tissues may be insufficient to clear up the condi-

tion completely" If we may assume that the acidosis in the 2 cases herewith reported was due to these unknown organic acids, then this contention of Starr and Fitz is untenable, for Case I received very little soda and Case II none at all

The following 2 cases illustrate another difficulty, namely, that we may have glycosuria and hyperglycemia without diabetes

Case III—Mrs J C C, No 2169, age forty-three. She had always been subject to headaches, but had had them more frequently in the ten days previous to the onset of the present illness On November 27, 1923 she went to bed with a very severe headache, the worse she had ever had About 2 30 the following morning her husband was aroused by a noise from the patient like one in a nightmare. He roused her with difficulty She complained bitterly of the pain in her head, said she was dying, and asked for the doctor From 3 30 A M she became more and more somnolent and was aroused with increasing difficulty The doctors who saw her that night and the next day at her home in a small country town found sugar in her urine, considered that she had diabetic coma and sent her to New Orleans where insulin was available She was admitted to the Touro Infirmary about 8 A M on November 29th When she was seen shortly after her admission she was lying upon her right side by preference She was somnolent but easily aroused and well oriented as to time and place, but did not know when she had been transported from her home Her chief and constant complaint was of headache There was a disagreeable odor to the breath, but it was not a typical acetone odor The patient was well nourished and developed The head was retracted and the neck was rigid and restricted as to anteroposterior movements and to some less degree as to lateral movements The pupils were equal, regular, symmetric, and reacted to light Knee-jerks were normal, plantar reflexes normal Kernig test was negative No paralysis of any cranial nerve Muscle power was intact everywhere The lungs were normal There was no hyperpnea The heart was normal Blood-pressure was 106 systolic, 58 diastolic Lumbar puncture showed spinal fluid under pressure Fluid in all four tubes was bloody Following the puncture she was somewhat relieved of her pain On November 29th Dr H N Blum reported retinal ecchymosis in left eye and on November 30th he reported some congestion of the optic nerve of the right eye, as well as some elevation and hyperemia of the left disk which, however, did not assume the proportions of a choked disk The urine showed no sugar, no acetone, no diacetic acid The blood-sugar was normal 110 mg per 100 c c of blood On December 1st lumbar puncture again showed the fluid very bloody The blood-pressure before the puncture was 140 systolic, 90 diastolic She continued to vomit from time to time and her complaint was of a drawing feeling in the back of her neck and of general discomfort A positive Kernig sign had developed on both sides, slightly greater on the left By December 5th patient had improved considerably and no longer complained as much of the head-

ache On December 7th she said she had too much energy to remain lying Meantime her own doctor had reported that he had found 2 per cent sugar in the urine on the first day of her illness and it was learned that sugar had been found in the urine one year previous at a life insurance examination Repeated urine examinations in the hospital, however, showed no sugar in the urine On December 10th at 1 A M, while she was asleep, she began to make queer breathing noises She became rigid, especially on the right side The respiration fell to 3 per minute, the pulse was between 60 and 70 When I saw her at 2 A M she was completely comatose, breathing stertorously, 20 per minute The pulse was 60 The mouth was half-open, the tongue slightly protruded, with much mucus coming from the mouth She occasionally made a few movements as if to vomit Presently the respirations fell to 6 to 10 per minute, became very irregular as to rhythm and as to depth The pupils were still equal The knee-jerks were exaggerated on both sides, ankle clonus was present on both sides The left arm dropped more helplessly than the right Her temperature rose steadily, reaching 107° F before her death, which occurred at 2 20 P M, December 12th The autopsy showed an extensive hemorrhage in the left optic thalamus, relatively old, and free blood in the lateral ventricles There was a large amount of free blood at the base of the brain Urine drawn by catheter in the last hours of life had shown sugar present Other laboratory reports are given below

November 29th,	Spinal fluid	Culture negative Wassermann negative Fluid contained blood
	Blood	Carbon dioxid combining power of the plasma, 7.9 volume per cent Total non-protein nitrogen, 28 mg per 100 c c of blood Dextrose, 110 mg per 100 c c of blood
December 1st,	Blood	Total leukocytes 9500 S M, 13 per cent L M, 4 per cent N, 82 per cent E, 1 per cent
December 5th,	Blood	Total leukocytes, 10,500 S M, 14 per cent L M, 7 per cent N, 79 per cent E, 0
November 29th,	Urine	1017 acid, albumin 0, sugar 0, acetone present, indican trace Sediment negative
November 30th,	Urine	24-hour specimen 300 c c, 1014, acid, albumin 0, sugar 0, acetone trace, indican 0 Only an occasional pus-cell and epithelial cell No casts nor red blood-cells

*Summary*—A patient in whose urine sugar had once been found developed a coma characterized by severe headache and retraction of the neck and vomiting. The urine showed sugar for a few hours. Subsequently the blood-sugar was normal. There was no acidosis. The spinal fluid was bloody. After a lucid interval of nearly ten days she again went into coma with signs of further intracranial damage. In this coma, glycosuria was again present. Autopsy showed extensive cerebral hemorrhage at the base of the brain and into the ventricles.

Case IV—Miss M. B., No. 2223, age forty-five. On August 9, 1924, about 8 P. M., she was telephoning. While apparently still in good health she yielded the telephone to a friend. Suddenly she began to vomit and within a few minutes was unconscious. She was immediately brought to the Touro. The urine drawn by catheter showed sugar, but *no acetone, no diacetic acid, no albumin, no casts*. The blood-sugar was 200 mg per 100 c.c. The patient was entirely unconscious. Physical examination showed nothing noteworthy beyond an enlargement of the heart to the left and a blood-pressure of 198 systolic, 100 diastolic. The lumbar puncture was done under great difficulty because of the struggling of the patient. The fluid obtained was under increased pressure and was bloody. On January 10th she was easily roused and was very willing to talk. She was only partly oriented and seemed to have a great deal of trouble in answering questions. During her stay of a month in the hospital the disorientation continued and she was amnesic. The pupils became unequal, the left being larger than the right. There was a left external rectus paresis. A marked Kernig developed on both sides. For a while she voided urine involuntarily. About February 12th she was allowed to go home. It was reported that she was doing well and that her mental condition had improved considerably. On February 17th at 4:30 A. M. she was heard breathing stertorously and her family found her completely unconscious. She was then at once brought back to the hospital. At 6:30 that morning her blood-pressure was 230 systolic, 120 diastolic, pulse 120, irregular in volume as well as in rhythm. The urine showed no sugar, no albumin, no acetone, no diacetic acid, many red blood-cells. Lumbar puncture showed spinal fluid under pressure with much blood. After lumbar puncture blood-pressure fell to 120 systolic, 80 diastolic. Five minutes after the puncture the stertorous breathing ceased and for several minutes only one respiration for several minutes was taken. Respiration ceased entirely for four minutes before the heart stopped.

Autopsy showed the dura bulging with a small amount of free blood over the superior surface of the brain. The veins of the brain were considerably distended, appearing as dark blue tortuous lines in the pia-arachnoid. At the base of the brain was found a considerable amount of free and recently clotted blood. This blood was most prominent on the under surface of the frontal lobes, extending backward to the optic commissure. The



vertebral, basilar, internal carotid, and anterior cerebral vessels showed a number of arteriosclerotic plaques in their walls. The general outline of the brain was disturbed, this was particularly noticed in the cerebral hemispheres. The right hemisphere was bulging very markedly forward, but most strikingly to the middle line, and had encroached upon the left hemisphere, producing a displacement to the left. The two hemispheres were held together by recent hemorrhage. On palpation the cerebrum was fluctuating. On section there was found, about 1 cm. beneath the cortex, well clotted blood which had destroyed most of the white structures. This blood was found to extend back on a line with the fissure of Sylvius and in that area was beneath the floor of the right lateral ventricle, it encroached upon the structure to a slight degree and had, by pressure, destroyed the structures of the left cerebrum to a less degree. There was a small amount of hemorrhage in the left ventricle. A study of this blood showed that some of it was old clot, whereas most of it was liquid blood as the result of a recent hemorrhage. The kidneys showed a chronic interstitial nephritis and an acute hemorrhagic nephritis.

*Summary*—A sudden coma in a patient previously known to suffer from hypertension was characterized by glycosuria and hyperglycemia. There was no acidosis. The spinal fluid was bloody. There were many indications of cerebral damage. After an interval of a month another cerebral hemorrhage resulted in death. Autopsy findings were very much as those in Case III.

These 2 cases illustrate again the long known fact that lesions at the base of the brain and particularly in the fourth ventricle produce a glycosuria. This recalls the classical piqûre experiment of Claude Bernard. It is thought that the impulse passes along down the sympathetic to the liver and the latter organ, under influence of the abnormal stimulation, yields to the blood-stream an undue amount of its stored glycogen. The blood-sugar in this way is raised above the normal threshold of the kidney and the excess overflows into the urine. It was not surprising, therefore, that in Case IV we found a hyperglycemia and, if the blood of all of these cerebral cases with glycosuria were studied, a hyperglycemia would always be found. Misleading as the finding of a high blood-sugar and sugar in the urine was, there existed no real difficulty in the diagnosis in these 2 cases. In the first place the history in both instances pointed away from and not toward diabetic coma. There had been no symptoms characteristic of diabetes. The onset of the

coma had been dramatically sudden, particularly in Case IV. Diabetic coma usually has warnings as, for example, the hyperpnea, the gradual increasing drowsiness, etc. The diagnosis of intracranial pathology was easily established once the bloody spinal fluid was obtained. This is a procedure that should always be carried out in cases of coma. Once we were aware of the intracranial disease, we were no longer likely to be misled by the hyperglycemia and glycosuria, for we could then attribute to them their proper value.

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## CLINIC OF DR O W BETHEA

### CHARITY HOSPITAL

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#### PLEURISY REMOVAL OF SEROUS FLUID

WHILE pleurisy is one of our most common diseases, there is still much difference of opinion as to many phases of its management. This particularly applies to the removal of serous effusion. We are yet trying to decide such questions as when to resort to aspiration, what apparatus to use, how to carry out the process, how much fluid to remove, the after-care of the patient, and numerous other details of more or less importance. A discussion of these points is always of interest, even if little that is new or original is brought forward. I will make no effort to cover the entire subject, but merely try to present some points of particular interest.

Preliminary to taking up the discussion of the removal of this fluid I wish to pay a passing tribute to the matter of "exploratory punctures." By this I mean those punctures that are made merely to secure a specimen for investigation in order to establish a diagnosis and direct therapeutic measures. The protest I wish to offer is this—when aspiration is done at all every facility should be ready to remove any fluid that may be found that would require removal. Failure to do this would be very much in the same category as would making an exploratory incision in the abdomen to see if the patient had appendicitis with the intention of coming back at a later time and removing the appendix should trouble be found. In other words, the surgeon in abdominal work should be prepared to do whatever is indicated, and when the operator goes into the chest for fluid he should be prepared, also, to meet any requirements.

When to operate is often a problem requiring much judgment and careful consideration. In a general way I believe the following are, at least, among those indications that justify aspiration.

- 1 It may be advisable in order to establish a diagnosis that intelligent therapeutic measures may be employed. As stated previously, when aspiration is resorted to under these circumstances the operator should be prepared to remove a sufficient amount of fluid that may be found.

- 2 If there is enough fluid present to directly cause trouble, such as interference with the circulatory function or damage to the lung through pressure.

- 3 If there is a possibility of pus, as would be indicated by chills, sweats, fever, etc.

- 4 If the apparent level of fluid is rising in spite of all efforts at treatment.

- 5 If there is an appreciable amount of fluid present and it is remaining stationary in spite of all efforts at treatment.

In establishing the two last findings considerable care is required, and I wish to state briefly a few points that have been of value to me.

We should always have the patient in the same position for examination. It is naturally the case that if the patient leans farther forward upon one examination than upon another it may, to a certain extent, affect the level of the fluid in the chest, no matter what its character. It has been my rule to try to establish the apparent level of the fluid in the back and record this finding, using some landmark, as a scar or a mole, the level of a certain spinous process, or the border of a certain rib. Then in each subsequent examination the patient is placed, as far as possible, in the same position, and, with my eyes shut, the line is found by percussion, palpation, and auscultation separately. Of course, many other factors must be taken into consideration in establishing each part of a diagnosis such as this.

When aspiration is found to be necessary another important consideration is how much fluid to remove. We know that we cannot remove it all no matter how carefully the process is carried

out, and we know equally well that in a rather large percentage of cases this remaining fluid is absorbed. In deciding how much to remove we must give due attention to several factors. One of these is the amount of fluid present, the more fluid present, naturally, the more we would expect to remove with safety. If one patient has 2000 c c and another 1000 c c, we would probably remove much more from the first. Another consideration is the reaction of the patient to the operative measure. This will be discussed later. Whether the fluid is in the right or left side must also influence us in this matter. In my personal experience it has seemed to me quite definitely established that we can remove a larger amount of fluid with safety from the right side than from the left, that is, of course, due to the relation of the left-sided effusion to the heart. This organ may have adapted itself, to a large extent, to the pathologic condition and a sudden relief has a greater tendency to produce circulatory disturbance.

If seropurulent fluid is found, it is probably best to remove as much as is possible, the operator being guided, of course, by the reaction of the patient. I might say in passing that if there is any one fact relating to this subject that seems to have been clearly settled by recent statistics, particularly those accumulated during the recent war, it is the value of repeated aspirations and delayed resection, if any, in purulent pleuritis.

As just stated, one of the factors governing the amount of fluid to be removed is the reaction of the patient. The careful clinician of today does not unnecessarily undertake an operation of this kind without sufficient assistance to enable him to keep the patient under a careful observation during the process. Among the indications for suspending, or immediately discontinuing, aspiration are: A decided change in the pulse rate or character, a marked fall in blood-pressure, cyanosis, vertigo, nausea, violent coughing, or any other evidences of shock. Not only should these be looked for, but facilities should be at hand for proper handling should trouble develop. Some of our leading medical men advise keeping a blood-pressure apparatus on the arm of the patient and taking a reading every few seconds.

This is particularly desirable where the effusion is in the left side

Let us now discuss some of the more important phases of the technic of the measure under consideration. Before beginning the actual operation, every part of the apparatus should be thoroughly tested out. There are few things more embarrassing than to have the instrument (needle or cannula) introduced only to find that the rest of the outfit will not work properly. I have had this humiliating experience one time, and since then I have avoided a recurrence by the plan I have suggested here.

It is almost needless to say that every phase of the operation should be carried out with the strictest aseptic precautions. In a hospital this is comparatively easy, in the home with sufficient trained attendants it offers few problems, but very often this measure must be carried out in the home with very limited facilities, in which case only the most painstaking care on the part of the operator can insure proper protection to the patient against infection. Under all circumstances the operator should wear a gown, sterile gloves, and have the assistants thoroughly understand the part they are to perform before the operation begins.

The best position of the patient is sitting up in bed with the body leaning forward. I prefer the bed to a chair for the reason that it is so much easier to dispose of the patient should unfavorable symptoms develop. When the patient sits in bed the affected side should be toward the edge of the bed so it can be more easily reached. When for any reason it is considered undesirable for the patient to sit up, a recumbent position or a semirecumbent position will answer well. In using one of these positions the patient should probably best lie on the well side with the back toward the edge of the bed. In any event the arm on the side of operation should be raised, sometimes it is of advantage to have the patient grasp something stationary to hold the arm in place. The body should be slightly bent toward the well side. These measures give more freedom to the operator and tend to widen the intercostal spaces.

In preparing the patient we should not overlook the value of suggestion. We can get much better co-operation and have much less tendency to shock if the patient is put in a proper mental attitude by assurances as to the absence of material discomfort and a cheerful prognosis in general. It is usually best to administer a stimulant, such as 4 c c of aromatic spirits of ammonia, and this should always be available in case of need. A cup of coffee will answer the purpose well.

The field of operation should be thoroughly cleansed, the surrounding area protected with sterile towels, and a sufficient surface covered with some disinfectant, as tincture of iodine.

A local anesthetic should always be employed. It secures better co-operation on the part of the patient, lessens the tendency to shock, and as a general consideration pain should always be avoided when it is reasonably possible. Probably the most satisfactory is  $\frac{1}{2}$  to 1 per cent solution of procaine (novocain). The anesthesia should be both superficial and deep.

In selecting a site for the puncture we have to be guided by the amount and position of the fluid. In a serous effusion of sufficient amount to require removal probably the best site is the midscapular line about the eighth intercostal space. There is no intention to arbitrarily fix this site.

After there has been sufficient time for the anesthesia to have effect the aspirating instrument should be introduced with a firm steady movement just over the top of the rib, thus lessening the chances of damaging the intercostal artery.

The outfit that I have found most satisfactory consists of the following:

A trocar and cannula, the latter about 13 gage. This is made to fit the Luer syringe. The trocar should fit smoothly and the instrument, when put together should not present a shoulder or bulge, where the point of the trocar ends and the cannula begins. I can possibly better show this by an enlarged exaggerated illustration, than describe it (Fig 172). The instruments should be highly polished and the trocar should be sufficiently sharp to enable its being easily introduced but the



point should not be sharp enough to increase the possibility of injury to the visceral pleura or the lung

A Luer syringe (all glass), the 20-c c size, meets every requirement and fits the standard Luer needle

A Potain vacuum bottle outfit adapted to fit the Luer needle (or cannula) instead of the standard Potain needle There should be two bottles so that when one is filled it can be emptied and the foam rinsed out, or removed with alcohol, while the other is being used

The good points of this apparatus are many To begin with there are many advantages of the trocar and cannula over a needle, and no disadvantages that I can think of just now



Fig 172 —Proper and improper types of trocar and cannula

If the trocar and cannula, as described above, are the proper size, they can be introduced with just about as much ease as can a needle

There is less chance of the cannula being stopped by a plug of tissue, if introduced with the trocar in place On the other hand, I have seen operators make an incision with a small lance before introducing a needle, with the explanation that it lessened the chance of the needle becoming plugged with tissue

There is certainly less danger of injuring the intercostal artery or any other blood-vessel There is also less danger of injury to the visceral pleura No matter how carefully a needle (or cannula) is introduced, as the fluid is withdrawn and the lung approaches the chest wall, the point of the instrument is bound to come in contact with the visceral pleura The respiratory movement increases the danger of injury by dragging this surface against the point of the instrument If the instrument is a sharp needle, some damage is almost certain If the instrument is a blunt pointed cannula (from which the trocar has been removed), the danger of injury is negligible I can

remember in my early experience that we expected a certain amount of respiratory pain toward the close of the operation, and frequently the latter part of the material withdrawn was blood stained, and I believe that we got an unnecessarily large percentage of purulent fluid on subsequent withdrawals. When the pleura is lacerated by the point of a needle it not only furnishes a point of lowered resistance, but, if the damage is sufficiently deep, organisms may be admitted from the bronchial tubes.

There is less danger of damage to the lung, with the resultant possibility of pneumothorax, empyema, or hemorrhage.

With the smooth-pointed cannula, from which the trocar has been removed, it is much easier and safer to explore in different directions should fluid not be found at first.

Taking this outfit as a whole, we might claim certain advantages. When the trocar and cannula is introduced and the trocar removed, if serous fluid comes through, as it often does, the suction bottle apparatus is attached and the removal proceeded with. If the fluid does not come through, the Luer syringe is attached and suction made. Theoretically, any degree of suction can be made with this air-tight instrument. If the fluid is found to be of such a character that the Potain bottle can remove it, one Luer syringe is saved for examination, and then the Potain apparatus attached. If at any time the flow in the bottle should be stopped, it is disconnected and the Luer syringe attached. Should the cannula become stopped with a plug of more solid material the bottle is disconnected and a little air is blown through the cannula with the Luer syringe.

It might be argued that there would be too much danger of introducing air through these changes in connection. With an instrument of this size the amount of air that could possibly get in is negligible. If the patient will forcibly exhale and then wait while the connection is being changed the chance of air getting in is further reduced. Again, if there has to be any delay in making a connection, the end of the cannula should be covered with the gloved thumb. If there is any doubt about the thumb being sterile, it should be touched with iodine.

As previously suggested, one syringeful of the fluid should be saved for examination. This should never be neglected at the first aspiration. Sometimes where there is thick pus present the Luer syringe may fail to remove any appreciable material into the syringe, still there may be some in the cannula, therefore, when a puncture is apparently dry, the end of the cannula should be closed as it is removed and then air blown through it in the hope of getting sufficient material for diagnostic purposes.

The puncture wound should be touched with iodine, compressed for a minute or two, then the surface cleansed and the wound covered with a strip of sterile adhesive. This should be removed in a few hours and the lesion dressed with a small piece of gauze held in place with adhesive.

After the removal of the fluid there is rather a tendency for us to feel that we have done everything possible for the time being. There seems to be considerable difference of opinion among the various writers upon this point. Personally, I am of the opinion that we can possibly do much to facilitate the absorption of the remaining fluid and to prevent its recurrence. To this end I carry out very much the same measures that I would for fluid elsewhere in the body. This includes the employment of a salt-poor diet, at least the moderate limitation of liquids, sufficient covering to keep the skin active, some attention to diuresis, the use of mild hydragogue purgatives, rest, particularly for the benefit of the circulatory apparatus, and stimulation.

What to use as a stimulant, and how much, must depend, of course, upon the condition of the patient. Digitalis and strychnin probably meet the requirements as well as anything available. Digitalis may, also, in some cases, serve for diuresis. I have usually given about 1 c c each of tincture of digitalis and tincture of nux vomica three times a day. I realize that this may be open to criticism, in fact, it is argued that none of these measures may be of value for removal of fluid of this character. We can only fall back on that rather vague and indefinite quantity, "clinical experience."

In after-care of these cases of the so-called primary type we are rewarded in the majority of instances by seeing the remaining fluid disappear, with proper general care, and the patient return to an apparent normal. We must consider, however, the established fact of the large percentage of tuberculous infection that is found to be the etiologic factor. It is well, therefore, to consider any case of pleurisy with serous effusion as probably tuberculosis, and manage accordingly. This requires, among other things, repeated examinations over a long period of time. My usual rule is a thorough examination every three months for three years. Not only this, but the patients should have the benefit of having their lives directed in such a way as to bring them up to and keep them in a high state of physical excellence. Diplomacy and common kindness are often needed in acquainting those concerned with the prognosis.

My plan has been to wait until the acute condition subsides, then go to the home and, in the presence of responsible members of the family, plainly state the facts and make my recommendations as to the future. The patient should be given the benefit of a cheerful outlook, but at the same time must learn the paramount importance of protecting himself and others. I can look back upon many cases where the occurrence of this disease has been one of the most fortunate happenings to many individuals, for, as a result of it, their lives have been so ordered as to bring them up to and maintain them in a state of well-being that previously had not even been within the range of their knowledge of the possibilities.



## CLINIC OF DR HENRY DASPIT

### CITY HOSPITAL FOR MENTAL DISEASES

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#### A CASE OF SYPHILITIC LEPTOMENINGITIS TREATED WITH TRYPARSAMID

THE great penalty paid by the infected individual as the result of improper, hesitant, and too often routine treatment of syphilis of the central nervous system prompts me to bring this case before you today. Though we are unable to present a complete restoration of this man to his usual normal status, much may be gained.

You will hardly recognize this man as the patient you have previously observed—on two occasions—in the Neurological Service of the Charity Hospital. He now enters the room with quick step though of somewhat downcast eyes and stolid expression. He greets the examiner with a quiet “Good-morning,” and in reply to inquiry states that he feels well. On closer scrutiny, you will observe that there is a generalized lowering of all his mental faculties without any evidence of psychotic formulations. He is placid and somewhat unproductive unless prodded. Nevertheless, this indifference to surroundings is much more apparent than real, as we have frequently had occasion to observe spontaneous remarks which indicate that little passes unnoticed. This morning when told that he was to be transferred to the State Hospital he seemed pleased and stated that he would see So-and-so, naming almost every male transferred during his time of residence here. There is very little in his mental make-up that would mark him as parietic and, if the expression may be used, his present mental status is that of an acquired imbecility—an organic dementia which has struck apparently evenly his emotional and intellectual spheres.

In tracing our knowledge of this case, we note that he has never married and is now twenty-five years of age. Inquiry

shows nothing in his progenitors that could have any possible bearing on his present illness. His birth and early life were quite uneventful. He walked and first spoke at about the end of the first year. General health has been excellent. He is reported as having been an average pupil and to have completed the graded school work. No evidence of neurologic or psychiatric disorder until leaving the U S Navy in which he served during the World War. It was during this time that he acquired syphilis. He was then noted to be "nervous, suffering with persistent headache, and indifferent as to working." He entered a service hospital where it was recognized that he was luetic and it is reported by his family that he received two courses of salvarsan and mercury. You will now recall that when he first came under our observation in July, 1923, he was presented to you. He then entered the hospital as he had experienced several, not closely associated, epileptiform seizures. At that time he was slightly confused, well orientated, and knew that he was ill. He complained of persistent head pain radiating into the upper cervical region bilaterally. His pupils were inactive to light and active on accommodation. Slight nystagmus (spontaneous) was observed, that increased on lateral vision. Lingual and digital tremor were present. There was no material speech disturbance other than a very slight bradylalia. The knee-jerks were not elicited or was there any pathologic skin reflex. As the patient was confined to bed, gait could not be tested. The blood-serum and spinal fluid showed a strongly positive Wassermann reaction. The spinal fluid, slight blood contamination, contained 500 cells and gave a very heavy globulin reaction. Gold sol was not reported. During his stay in the hospital he received eight neosalvarsan intravenous, twenty-four deep gluteal, injections of mercury biniodid, and potassiumiodid by mouth. His condition was much improved and he was referred to the out-clinic for continuation of treatment. He left the hospital August 30, 1923. Nothing further was seen of the patient who failed to report to the out-clinic until November 20, 1923, when he was again admitted to the ward comatose and in severe epileptiform attack. The convulsive movements and uncon-

sciousness continued from 7 A M until 9 P M The spinal fluid (this time without blood contamination) showed a strongly positive Wassermann reaction, 300 cells, and a very heavy globulin Urine examination gave a gravity of 1030 and 3 per cent sugar Blood-sugar, 400 mg per 100 c c Mercury by inunction and potassium iodid by mouth was pushed After receiving four days of mercury and potassium iodid, neosalvarsan was added and followed by spinal drainage There was slight temporary betterment, but, irrespective of therapy, the epileptiform seizures increased in frequency and he rapidly depreciated He became wet and dirty in his habits, drooling, and speechless There was rapid loss of weight He was constantly in bed

He was removed to the City Hospital for Mental Diseases on January 2, 1924 In this institution he continued to deteriorate and the epileptiform seizures were of frequent occurrence By April he was having from two to three spasming seizures daily and was looked upon as a hopeless, inert, untidy dement It was at this time that the first tryparsamid for experimental use was received by the University from the Rockefeller Institute for Medical Research As no demonstrable contraindication to its use was found and though the patient was a most unpromising prospect, treatment was begun Mercury salicylate, 0.0972 gm, by deep gluteal injection, and tryparsamid, 1 gm per 22.55 kilos of body weight, in 10 c c of distilled water intravenously, were given at weekly intervals He received a total of 72 grams of tryparsamid and 2.8 grams of mercury salicylate It is unnecessary to follow his progress in detail, but I would remark that following the first dose of tryparsamid the epileptiform seizures ceased completely His physical improvement has been definitely progressive and he has gained a bit over 15 kilos in weight He is now tidy in his habits and somewhat interested in his personal appearance He bathes and dresses himself He is employed in light work, brass polishing, room-cleaning, and minor errands on the ward His mental age is found to be about nine years There is not sufficient in the psychiatric survey to justify an opinion that he is definitely psychotic The spinal fluid as reported from our laboratory before the em-



ployment of tryparsamid showed Wassermann 4 plus (0.5 c.c.), cells 215, globulin 4 plus, gold 4554321000, now shows Wassermann negative, cells 7, globulin trace, gold 2222110000. The urine is sugar free and the blood-sugar within normal limits.

It should be apparent to you that the first therapeutic attack in this instance fell far short, and that treatment was continued along the same lines too long. His prompt response to tryparsamid was startling, and had it been practical to initiate this form of therapy sooner there is no doubt that the mental dilapidation which is regarded as the result of gross cortical changes that were secondary to the syphilitic leptomeningitis would have been offset. It has always been found to advantage, in that it lessens the tendency to unfortunate reactions to the arsenical, to employ brisk mercurialization before using any arsenic compound. In this clinic the procedure is routine, and we believe that the combined use of arsenic and mercury in the treatment of neurosyphilis offers most to the patient. It is naturally quite impossible to definitely place before you a scheme that would be of use in all cases. Dosage and various modifications in technic must be left to your judgment in your later study of the special needs of the individual case. In these cases of acute meningeal syphilis prompt response to treatment is essential and any real delay in betterment should be regarded as an indication of improper therapy or the presence of a neurotrophic organism highly tolerant to arsenic. Our apparent disregard of the glycosuria and the hyperglycemia was not an oversight. We had seen the patient many times before these findings took place, and our knowledge of the case did not indicate any pancreatic background. Also, it has been our experience to find an increase in blood-sugar in these intense spasming states incident to syphilitic brain disease. Here as in other instances the sugar came within normal limits, as the convulsive seizures lessened in response to antiluetic treatment.

Four months after presentation of the patient he continues to be sugar free. His spinal fluid Wassermann is negative, cells 7, globulin negative. The gold reaction is showing a gradual return to a rather typical parietic curve.

# CLINIC OF DR GEORGE R HERRMANN

## CHARITY HOSPITAL

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### THE UNUSUAL MANIFESTATIONS OF HEART DISEASE

Classification, Illustration, Explanation, Differentiation, and  
Alleviation or Treatment of These Symptoms  
Affirmation of the Value of Electrocardiographic Studies

IN this and subsequent hours I wish to call to your attention and illustrate with case histories the not infrequent presenting symptoms and signs of heart disease, which all too often lead to erroneous diagnoses with inevitably serious consequences. This will meet with the more or less justifiable objection to the singling out of atypical symptoms at the expense of the more common typical symptoms of an affection. The usual manifestations, however, of heart disease, namely, dyspnea on exertion, palpitation, edema and cardiac pain, need no especial emphasis since they are correctly interpreted by even the inexperienced physician. The unusual symptoms, on the other hand, tax the acumen, ingenuity, and diagnostic resources of the experienced clinician. The occasional unsuccessful laparotomy for an acute abdominal pain in a case that later proves to be suffering from heart disease, and the all too common fatal issue in cardiac cases, fallaciously reported as acute indigestion, emphasize the importance of accuracy in diagnosis.

The atypical symptoms of heart disease may be grouped in a number of ways. Let us first consider the unusual clinical manifestations that may occasionally appear in the pathologic processes most commonly associated with these protean symptom complexes.

## I Coronary Artery Disease.

- (a) Thrombosis with cardiac infarction
- (b) Sclerosis with or without angiospasm

Conditions presenting sudden severe sharp upper abdominal pain, nausea, vomiting, collapse, abdominal tenderness, and a vague mass, rigidity, fever, and a leukocytosis, thus simulating an acute surgical condition, such as a perforating gastric or duodenal ulcer, a ruptured gall-bladder, an acute pancreatitis, an intestinal obstruction, or a mesenteric thrombosis

Or conditions presenting the picture of a chronic gastrointestinal lesion, with a more or less constant dull ache in the right upper quadrant or epigastric distress and distention, gaseous eructation, and anorexia, often diagnosed as chronic indigestion, dyspepsia, or gastritis, may be encountered

## II Myocardial Insufficiency, Chronic Myocarditis

- (a) Congestion
- (b) Edema

Conditions presenting a constant dull right upper quadrant or epigastric distress and distention, gaseous eructation, nausea, vomiting, and at times jaundice

Or conditions presenting asthmatic attacks at night, a cough and expectoration that is at times blood-streaked, along with râles, altered breath sounds, and impaired resonance at the bases of the lungs, may be encountered

Mental symptoms, such as confusion, hallucinations, delusions, or even depressive or maniacal psychotic states, are occasionally disturbing

## III Aneurysms—Sacculated, Diffuse, or Dissecting

- (a) Laryngeal or tracheal obstruction
- (b) Bronchial or pulmonary compression

Conditions presenting vocal cord paralysis from the pressure on the recurrent laryngeal nerves or tracheal and bronchial obstruction from pressure, with atrophy and collapse of the cartilaginous rings of the wall, may be encountered

Or in rare instances dissecting aneurysm, presenting acute abdominal symptoms, may be subjected to unnecessary laparotomy

#### IV Acquired or Congenital Valve or Septal Lesions

(a) Mitral stenosis may cause a chronic cough, hoarseness, aphonia, hemoptysis, malar flush, signs of increased density at the left apex with râles at times simulating pulmonary tuberculosis, embolism, pulmonary, with signs suggesting pneumonia, or cerebral with hemiplegia, may be presenting syndromes

Tricuspid stenosis may present an enlarged liver and spleen and ascites, a picture in many respects identical with that of chronic adherent pericarditis, both of which conditions are not infrequently diagnosed as Banti's syndrome or cirrhosis of the liver

(b) Defective interventricular septum may cause a chronic cough, hemoptysis, and show very suspicious pulmonary signs due to the extreme congestion that may be present, thus making tenable the diagnosis of pulmonary tuberculosis

#### V Sudden Changes in the Cardiac Mechanism

(a) Paroxysmal auricular fibrillation

(b) Heart-block

These disturbances coming on suddenly are often accompanied by abdominal symptoms which are occasionally acute, with epigastric pain, nausea, vomiting, fever, leukocytosis, and at times also jaundice and hematemesis

#### VI Endocarditis—Subacute Bacterial or Rheumatic

(a) Embolism and infarction

(b) Chronic sepsis and toxemia

Conditions presenting an acute splenic pain or renal colic with hematuria acute headache with or without hemiplegia

Or conditions presenting chronic splenic discomfort and splenomegaly or chronic renal insufficiency with or without uremia or chronic mental changes with clouding, confusion, and even psychoses may be found

Pulmonary infarction may be erroneously diagnosed pneumonia or an infiltrative lesion of the lung

Chills and fever may simulate typhoid fever, malaria, or any septic state as pyelonephritis

Severe anemia with a blood-picture of a high-grade secondary or even a so-called primary anemia is quite common

## VII Pericarditis—Acute Fibrinous

The clinical picture of acute appendicitis or perforated gastric ulcer may be reproduced by this condition in rare instances

After this survey we might regroup our unusual manifestations under the headings of the unusual manifestations themselves. In this shorter classification we would have one outstanding atypical symptom complex, that of *acute abdominal crisis*, which is reproduced by any of the pathologic processes outlined above. *Chronic abdominal disturbances* is next in order. The other, presenting symptoms in order, would be *pulmonary, renal, cerebral, hematologic, and septic* manifestations.

With this outline of the possible sources of error in the diagnosis of cardiac affections, we may proceed to the study of some cases that presented unusual clinical pictures. The cases emphasize the importance of the subject, set forth differential diagnostic points, and affirm the value of electrocardiographic curves, and suggest bases for the atypical manifestations and their treatment, which subjects will be discussed later.

**Case I.—Sudden Collapse With Symptoms and Signs of an Acute Abdominal Crisis in a Patient Who, on Closer Study, Was Found to Have Arteriosclerotic, Aortic, and Coronary Disease and Myocardial Changes With no Abdominal Pathology Other Than an Engorged Liver.** Patient Died Suddenly Two Months Later.—T. M. P., a married woman aged fifty-four, was brought into the hospital in a state of collapse. During the latter half of a recital she had been seized with a sharp epigastric pain and a sensation of constriction. She had played two heavy numbers and was just finishing a light number when she sank to the floor unconscious. She had eaten only a light dinner. She had felt chilled on her way to the concert hall, and, on arriving, the hall had felt overheated. She remembered no prodromal symptoms. On regaining semi-consciousness, which was within a few minutes after the collapse, she was taken with *abdominal cramps* and a radiation of the pain to the back.

On arriving at the hospital she passed a copious soft stool, complained of nausea, and vomited. She vomited four times within a few hours, and the vomitus contained gross blood.

The pulse was rapid and thready. The *abdomen* was rigid, and an indefinite mass was felt in the epigastrium extending into the right hypochondrium. The leukocyte counts were 16,000 and 25,000 per cubic millimeter. The temperature ranged between 101° and 102° F. The blood-pressure was unobtainable. The urine contained albumin and leukocytes, but no casts or sugar.

At this point she was seen by the surgical chief, who considered the possibility of a perforated peptic ulcer, an acute pancreatitis or a pancreatic calculus, or a ruptured gall-bladder. He considered the patient in too profound a state of collapse to think of any surgical procedure.

The patient remained semiconscious throughout the night. She was given hypodermoclysis, 750 c.c. of saline under each breast, morphin, 8 mg subcutaneously, camphor 1 c.c. intramuscularly, and strophanthin, 0.5 mg

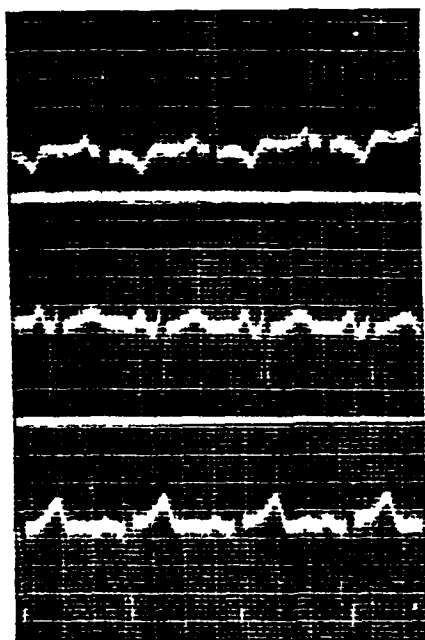


Fig 173—Case I. Electrocardiograms of Case I, Leads I, II, and III, from above down. These curves are definitely abnormal, showing conspicuous left ventricular preponderance with negative T waves in Lead I. The biphasic T waves with the left preponderance suggest a possible slightly defective intraventricular conduction (incomplete block) in the right branch of the His bundle. It is rational to infer advanced myocardial changes from these curves.

intravenously. Cheyne-Stokes breathing was noted, with the patient restless during the apneic periods.

The heart was found to extend 3.5 cm. to the right and 10 cm. to the left of the midsternal line on percussion. The heart sounds were distant and muffled and the muscular element of the first sound was noticeably decreased. The aortic second sound was hollow and slightly accentuated. A slight blowing systolic murmur was heard in the mitral and aortic areas. The

rhythm was regular. The lungs were resonant throughout, the breath sounds were harsh, and the expiratory murmur was prolonged. No râles were heard.

The next morning the patient was still prostrated. A distinct cyanosis was still present. The mass and rigidity were more definitely localized to the right hypochondriac region.

It was learned that she had had a similar attack of acute abdominal pain, diagnosed "torsion of the intestine" five years previously. She had developed an easily reducible hernia one year previously. She had always been "high strung" and had had a nervous breakdown. Her family history was negative except for the fact that her father had died of Bright's disease.

An *electrocardiogram* (Fig. 173) taken at this time was distinctly abnormal, with definite evidence of marked left ventricular preponderance and abnormal diphasic T waves which suggested defective conduction in the right branch of the His bundle.

With this evidence of cardiac pathology, an *x-ray plate* of the heart was taken at 2 meters. This showed enlargement of the heart and dilatation and calcification of the aorta. The transverse diameter of the heart measured 17 cm. and that of the aorta 7 cm.

The gastro-intestinal *x-ray* studies showed an enlarged liver and possible enlargement of the spleen, but no evidence of disease in the stomach or gall-bladder.

During her stay in the hospital the patient improved rapidly. The mass and tenderness in the abdomen disappeared. The fever and leukocytosis dropped to normal within three days. The blood pressure gradually rose from 150/100 on the second day to 210/140 on the eighth day and then dropped back to 200/120, where it remained. The albuminuria cleared up and the phthalein excretion was found to be 75 per cent in two hours. The blood Wassermann was negative.

She was discharged on the twentieth day with the advice that she must limit her activities considerably, otherwise she might expect further attacks, which might be of even more serious moment.

She died suddenly one month later when she was preparing to give another concert.

*Discussion*—This case was apparently one of acute abdominal crises in an extreme state of collapse on admission. The decision to wait and watch was a fortunate one. The *x-ray* and electrocardiographic evidence of heart disease gave the clue to the situation. The patient had had a coronary accident, which might have been due to actual thrombosis or may have been only the result of an angiospasm in a sclerotic coronary artery. She had had a previous accident of a similar nature that had led to the diagnosis of "torsion of the intestine." The extreme degree of circulatory collapse, the cyanosis, Cheyne-Stokes breathing,

rapid regular heart rhythm, with the distant heart sounds and especially the loss of the muscular element of the first sound, should have suggested the diagnosis immediately. The sudden death with the resumption of her activities, makes quite certain that she was suffering from coronary disease.

*Case II.—Sudden Severe Abdominal Pain in Attacks Simulating Gall-stone Colic in an Individual With Coronary Sclerosis, and Finally Coronary Thrombosis, Status Anginosus, and Death*—C S A, a housewife aged sixty-five, was brought into the hospital because of sudden severe sharp abdominal pain which radiated from the right hypochondrium into the left and into the back. She had had several short attacks during the night before admission. Similar attacks which had been considered "gall-stone colic" had been troublesome off and on for several years, but had never appeared in such rapid succession. The abdomen seemed to the patient to swell during the attack, to become board-like, tender on pressure, and sore. She felt faint during the attack, was nauseated, but did not vomit, had no appreciable fever, was never jaundiced, but noted a distinct polyuria following the attacks. At the time of admission the patient was in an attack and the routine history and physical examination were postponed. She was in evident agony. There was distinct tenderness, slight rigidity, and a vague mass in the right upper quadrant. The absence of fever and leukocytosis led to a further and more careful study.

This study yielded important diagnostic facts. The attacks, though not related to meals, were frequently brought on by excitement and exertion. There was also some shortness of breath and palpitation accompanying the pain. Furthermore, the cessation of emotion and activity, relaxation and rest, with a loosening of the clothing, would cause the attacks to wear off in fifteen to twenty minutes. In some attacks there was somewhat of a feeling of imminent dissolution, a rushing of blood to the head, dizziness, and tingling in the fingers. Occasionally there was a dry cough which persisted as long as the pain continued. The case thus took on an altogether different aspect.

The family and marital history contained no significant facts other than that the patient had had one miscarriage and had given birth to 6 children, all of whom she reared to adult life. Her past history gave no definitely relevant facts. She had always done hard household work.

The physical examination revealed a short, stockily built old woman with a florid complexion, a flush of the face extending down over the neck and dilated venules scattered over the malars. The carotids were throbbing.

The heart was not definitely enlarged. The apex impulse was in the fifth intercostal space, 10 cm to the left of the midsternal line. The impulse was heaving, but diffuse. The aortic second sound was accentuated and 'hollow'. The first sound at the apex was muffled. A blowing systolic murmur, audible at the apex, was well transmitted to the axilla and over the precordium. A short systolic murmur was heard in the aortic area. The



blood-pressure was 240/140 on admission. The lungs were slightly emphysematous and a few moist râles were heard at the bases.

The *abdomen* was slightly rigid and the tenderness was acute. The mass, which had become more definite, was apparently the lower part of an engorged liver extending 4 cm below the costal margin.

The *extremities* showed Heberden's nodes. The peripheral vessels were only moderately sclerosed. A slight edema was present about the ankles.

The x-ray of the heart was not diagnostic. The aorta showed a moderate arteriosclerotic knob, but no dilatation. The great vessels were 5 cm and the heart shadow 15 cm in transverse diameter.

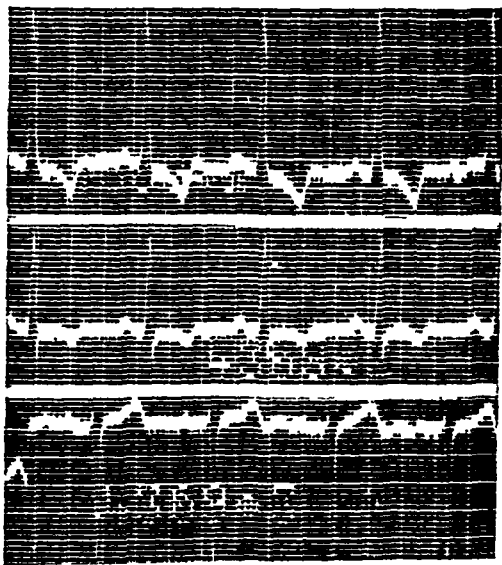


Fig 174—Case II. These curves show a very conspicuous left ventricular preponderance, negative T waves in Leads I and II of the character that one often gets in coronary occlusion. The slightly increased Q R S interval (0.8 to 1.0 sec) and the diphasic T waves indicate defective conduction (incomplete block) in the right branch of the His bundle. Severe myocardial changes and coronary disease may be inferred from these electrocardiograms.

The x-ray studies of the gastro intestinal tract revealed no evidence of organic pathology. The gall bladder detail plates were negative.

The *electrocardiograms* (Fig 174) showed definite evidence of grave myocardial changes. There was a very marked left ventricular preponderance with diphasic T waves in all leads and a slight widening of the Q R S interval. These signs indicate defective conduction (incomplete block) in the right branch of the His bundle.

The urine contained a slight trace of albumin and a few hyaline and granular casts. The phthalein excretion was 30 per cent in two hours. The

blood chemical studies showed no evidence of the retention of nitrogen bodies. The blood-counts and hemoglobin were normal and the Wassermann was negative.

The patient's attacks of abdominal pain were found to be relieved by nitrites, and with rest in bed the attacks gradually stopped. The blood-pressure dropped to 150/80 and the patient felt comfortable. She was discharged to her home on caffeine preparations and iodids. She remained free from trouble for a few months, and then she acquired a slight infection. During this infection she was seized with a sudden severe sharp pain in the precordium and in the left arm. This was her first pain above the diaphragm. Nothing would relieve the pain, which was accompanied by extreme orthopnea, an ashen pallor, and frothy blood-tinged sputum. The heart sounds were faint and the muscular element of the first sound was conspicuously muffled. Short attacks of tachycardia were noted. The patient remained in *status anginosus* for almost a month before she died suddenly, probably from cardiac rupture.

*Discussion*—The case is obviously one of coronary sclerosis which ended in thrombosis, myocardial infarction, and probably rupture. The acute abdominal symptoms were misleading only while the history and examination were incomplete. The lack of fever and the leukocytosis were clues that led to the more careful study. The electrocardiograms gave the most positive evidence of the source of the trouble.

*Case III.—Acute Attacks of "Colicky" Abdominal Pain With Accompanying Jaundice, in a Patient With Aortitis, Fusiform Aneurysm of the Descending Aorta and Aortic Regurgitation, but no Evidence of Gastro-intestinal Pathology*—H. T. E., a blacksmith aged sixty-two, came into the hospital complaining of attacks of sharp "colicky" pain in the pit of the stomach and right side and occasional jaundice. The attacks dated back four or five years, but had become much more severe and more frequent in the half-year preceding his coming to the hospital. He attributed the onset of his trouble to a glancing kick in the epigastrium by a mule five years before admission. The pain was colicky in nature and radiated from the midepigastrium into both sides, but especially to the right. There was no relation between the taking of food and the onset of the pain. The eructation of gas often accompanied the attack and occasionally vomiting relieved the attack. This was especially true when the attack came on in the afternoon. Jaundice occasionally followed the attack and persisted for a few days. There had been a loss of 30 pounds in weight in two years. The patient had developed an inguinal hernia three or four years previous to admission, but this gave him no pain or trouble, as it was easily reducible and easily retained by a truss. A hydrocele of the right testicle had recurred after tapping.

In his past history he had had all the ordinary diseases of childhood without complications. He had had diphtheria at sixteen years, smallpox at

eighteen, and malaria frequently. He denied having had any venereal infection. He had never married and his family history was unknown to him. He had been a "hard drinker" for many years. He had not been able to carry on his heavy work as lead miner or blacksmith for five or six years, because of his stomach trouble.

The *physical examination* revealed a well-built man with good musculature, but a pallor of the face. There was an arcus senilis. The pupils reacted to light and in accommodation. The carotids were throbbing vigorously. No tugging of the trachea could be detected. The *heart* was enlarged to the left with the apex impulse in the sixth intercostal space 13.5 cm. to the

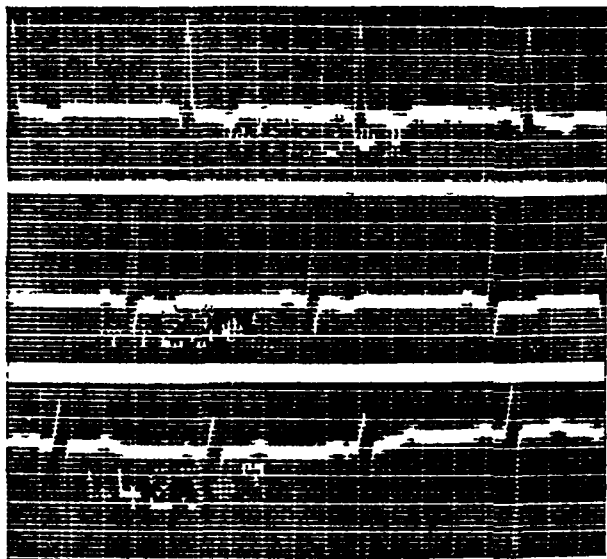


Fig 175—Case III. Moderate left ventricular preponderance, negative T wave in I and II. The slightly broadened Q R S interval (0.8 to 1.0 sec.) and diphasic T waves indicate incomplete block in the right branch of the His bundle. These are signs indicative of myocardial changes.

left of the midsternal line. The retromammary dulness was increased. A slight diastolic thrill was felt over the sternum and at the apex. The aortic second sound was absent and the pulmonary second sound was distinct. A long, high pitched aortic diastolic and a rough aortic systolic murmur were heard at the aortic cartilage. The aortic diastolic murmur was transmitted toward the apex, where its character was changed to a rumbling Austin Flint murmur by the functional obstruction to the mitral. A rough apical systolic murmur was well heard even in the axilla. The rhythm was regular and the rate was slow.

The brachials and radials were thickened, tortuous, and calcareous. Capillary pulsation was elicited. The finger tips throbbed. A pistol shot

sound and a diastolic Duroziez's murmur were heard on compressing the femoral with the stethoscope bell. The blood-pressure was 215/75 in the brachials and 245/70 in the popliteals.

The *abdomen* presented a liver that was palpable, but not tender, and a vigorously pulsating sclerotic aorta. There was an easily reducible right inguinal hernia and a right hydrocele. The prostate was enlarged and firm. There was no edema of the extremities. The reflexes were normal.

The hemoglobin and blood-counts were normal. The blood Wassermann was repeatedly negative. The urine contained a slight trace of albumin and a few hyaline casts. The phthalein excretion totaled 45 per cent in two hours.

An *electrocardiogram* (Fig. 175) was distinctly abnormal, with an extreme degree of left ventricular preponderance, diphasic T waves and a broadening of the Q-R-S interval, suggesting defective conduction, incomplete block in the right branch of the His bundle.

An *x-ray* plate of the chest showed a fusiform aneurysm of the descending aorta.

Gastro-intestinal *x-ray* studies failed to reveal any evidences of abnormality in the stomach, duodenum, gall-bladder, or intestines.

*Discussion*—This case, with only gastro-intestinal symptoms, showed on careful general physical examination the signs of chronic heart disease: aortic regurgitation, and aortitis. This emphasizes the value of a careful routine *general* examination in all cases. The *x-ray* examinations corroborated the physical findings and the electrocardiogram gave information that in itself would have turned the tide of the examination from the abdomen to the cardiovascular system.

Rest in bed, small doses of iodids, and tonic doses of digitals relieved the patient's symptoms. He remained fairly comfortable for about two years, when he died suddenly. The details of and the circumstances surrounding his death were not obtained.

*Case IV—Chronic Dyspepsia With Acute Attacks of Abdominal Colic in a Patient With Arteriosclerotic Myocardial Insufficiency and Heart block*—R. A. C., a physician, aged sixty-eight, presented himself for examination, because of a chronic dyspepsia, with much belching, abdominal distention, sourness of the stomach, attacks of abdominal colic, and tenderness in the right epigastrium and hypochondrium. The symptoms were not related directly to the taking of food. The "gas in the stomach" seemed to the patient to press up against the heart and embarrass it, as is often the case in hypersthenic individuals. The onset of the trouble had been insidious, with the dyspepsia dating back two or three years, but the "colicky attacks"

had been present for less than a year. He had had no nausea, vomiting, or jaundice. Fever and leukocytosis had never been noted. He had not been troubled with constipation or diarrhea and had noted no abnormality in his stools. Close questioning brought out the fact that he had suffered from attacks of dyspnea, which he had considered to be asthmatic. No edema had been noted.

His heart history revealed no significant infections, with a negative history in regard to venereal disease. Tobacco and alcohol had been used excessively throughout his adult life.

The *physical examination* revealed a moderately obese old man who was in evident agony with one of his attacks of abdominal colic. The pupils

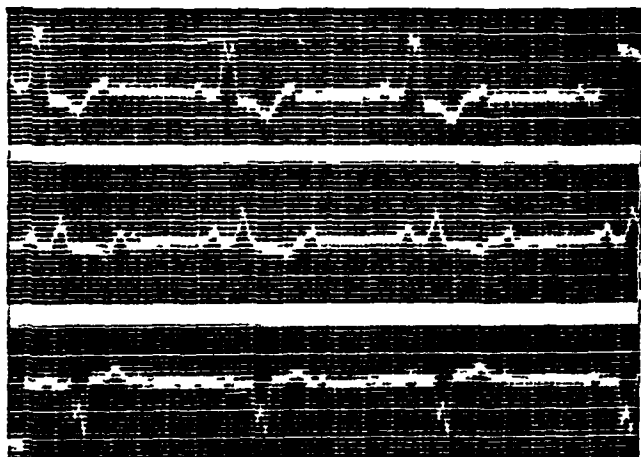


Fig 176—Case IV. Complete right bundle branch block Q R. S (11 to 12 sec) and 2 1 auriculoventricular block. These findings are pathognomonic evidence of severe wide-spread myocardial damage.

reacted to light and in accommodation. There was slight cyanosis and dyspnea. The neck veins were engorged.

The *heart* was enlarged, with the heaving apex impulse extending 13 cm to the left of the midsternal line. The retromanubrial dulness was increased. The rhythm of the heart was irregular at times and again quite regular, the rate was always slow, between 38 and 50 beats per minute. There was a rough aortic systolic murmur and an accentuated aortic second sound. The blowing mitral systolic murmur was well transmitted into the axilla. The first sound at the apex was muffled and blurted. Auricular beats could not be definitely heard. The blood-pressure was elevated 180/80, the high pulse-pressure being due apparently to the slow rate, for no aortic diastolic could be made out. The lungs were emphysematous and auscultation revealed many moist and bubbling râles at the bases.

The abdomen was rigid, but some of the rigidity was apparently due to voluntary protective spasm. There was definite tenderness in the right epigastrium and the right upper quadrant. A mass, presumably the liver, was felt along the right costal margin.

There was a slight edema of the pretibial tissues and about the ankles. The reflexes were normal and no evidence of Rombergism or of loss of sense of motion or position was found.

The urine contained albumin and casts. The blood was negative.

An x-ray examination of the gastro-intestinal tract showed the stomach in normal position, with hyperactive peristalsis, but no filling defect. The duodenum was also negative. There was no abnormal retention. An x-ray of the chest showed an enlarged heart and a broadened aorta.

The *electrocardiogram* (Fig 176) was conspicuously abnormal and gave evidence of very serious heart disease. There was auriculoventricular heart-block of a 2 to 1 type and complete right bundle branch block. These findings indicate a wide-spread myocardial lesion involving the main stem and the right branch of the His bundle.

Rest in bed relieved the patient greatly. He was able to get back to his practice, but fell dead in his office six months later, according to Dr Louis H. Behrens, who had referred him for electrocardiographic examination and who kindly furnished much of the history from his records.

*Discussion*—This patient presented a story of a more chronic type of gastro-intestinal disturbance, along with more recent acute attacks of colicky pains in the abdomen. The history of dyspnea, however, which was almost submerged, by the more prominent symptoms, gave the clue. The careful physical examination revealed more convincing evidence of the real cause of the trouble. The x-ray studies and especially the electrocardiograms furnished the evidence that clinched the diagnosis of arteriosclerotic heart disease, auriculoventricular and right bundle branch block, myocardial insufficiency or cardiac failure with congestion of the liver and abdominal viscera and slight edema.

*Case V—Chronic and Acute Abdominal Pain, a Tender Mass and x-Ray Evidence of Gastric Stasis (? Pressure) in a Patient With Slight Aortic Regurgitation and Bundle Branch Block. Patient Died on the Operating Table*—D. S. S., a retired merchant, aged seventy-four, was admitted to the hospital with the complaint of "agonizing" pain in the lower abdomen.

His present illness was taken up mainly with the account of symptoms of gastric origin which had begun a month before admission with a dull ache in the lower half of the abdomen. At first the pain was inconstant and not severe, but in the week before admission it had become constant and

agonizing. He had had no desire for food or water, both of which distressed him. He had had some nausea and vomiting, but no jaundice. He was constipated. During his present illness he had had three or four attacks of pain in his left chest similar to attacks that he had experienced between the ages of fifty-four to fifty-seven years. He tired very easily.

The family history was irrelevant except that the father fell dead of "heart failure" at seventy-four. The past history was important because of acute rheumatic fever for five months at the age of twelve years, and again for seven weeks at the age of seventeen, and again at fifty-four to fifty-seven. He had frequent acute exacerbations of four to five weeks' duration. He had erysipelas for four or five weeks at sixty-four. Besides the abdominal pain and the pain in the left chest, he had had severe pain in the left shoulder and arm. At seventy-two he had had acute urinary retention, at seventy-three he had another similar attack, and in this year he had had two more attacks. He had had diurnal ten to twelve times and nocturia three to four times for many years.

The physical examination showed "aortic facies," pallor, and marked carotid and subclavian pulsation, but no venous engorgement. The cardiac apex impulse was felt as a forcible thrust in the fifth intercostal space, 12 cm to the left of the midsternal line. No thrills or shocks were felt. The outer cardiac dullness by percussion was 3.5 cm to the right and 14 cm to the left of the midsternum. The aortic dullness was increased.

The heart sounds were slightly muffled. The first sound at the apex was replaced by a rough systolic murmur that could be heard all over the precordium and was well transmitted to the axilla. The systolic murmur at the base was more blowing in quality. A faint high-pitched diastolic murmur was heard in the aortic area after forced expiration. The second sound is reduplicated below the third costal cartilage, producing a protodiastolic gallop rhythm. The brachials and radials are markedly sclerosed. The pulses were equal, synchronous, of high tension, and somewhat collapsing. A capillary pulse was noted in the finger tips. The blood pressure on admission was 172/70, but dropped to 120/70. The lungs were negative except for râles at the bases.

The abdomen was slightly rigid and a firm, slightly nodular and very tender mass was palpable in the right upper quadrant, 8 cm below the costal margin. The mass was slightly movable. The stomach was dilated and gave a succussion note. There was a left inguinal hernia. The right testicle was enlarged. The prostate was broad and elastic. No median bar was present, but a neurogenic bladder was found on cystoscopy.

The extremities showed a slight amount of edema. The reflexes were normal. There was no Rombergism.

The urine contained a trace of albumin with rare hyaline and granular casts on one occasion. The output was low and the specific gravity was high. The phthalein excretion totaled 34 per cent in two hours. The blood examination revealed no abnormality. The Wassermann was negative.

A gastro-intestinal x-ray study showed an enlarged stomach with stasis due apparently to an organic lesion of the distal portion of the pylorus. The result of a pressure defect due to an enlarged liver was considered a possibility, but not a probability.

The x-ray of the heart showed some enlargement, the transverse diameter measuring 13 cm and the aorta 5.5 cm

The *electrocardiogram* (Fig 177) was conspicuously abnormal, showing broad diphasic complexes of complete right bundle branch block, the Q R S interval measuring 0.11 sec, the normal being at the most 0.08 sec., the P-R measuring 0.18 sec, which is the upper limit of normal. The rate was 75 per minute. The findings are those of a grave myocardial process.

The patient desired surgical intervention, but this was advised against because of the evidence of grave myocardial changes, and the evidence of beginning heart failure, with congestion and edema, and the possibility that the whole picture was due to the cardiac condition. Instead of following

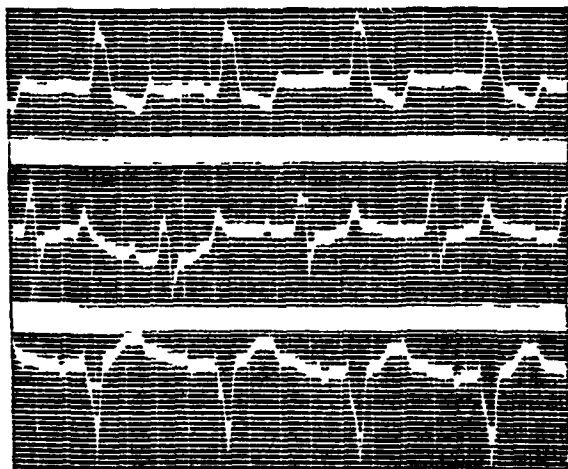


Fig 177—Case V. Complete right bundle branch block with Q R S interval of 12 to 14 sec and a P-R interval of 20 sec. These curves indicate myocarditis or myocardial lesions.

out the prescribed rest in bed and digitalization, the patient left the hospital and consulted an eminent surgeon, who considered operation advisable, as there was grossly very little wrong with the heart. Since, however, the patient had told him of our opinion, the surgeon decided to begin with local anesthesia. With the incision of the skin, the patient became pulseless and could not be revived—truly a surgical catastrophe.

*Discussion*—The case requires very little further comment. There may have been a gastro-intestinal lesion, but the cardiac condition, as revealed by the electrocardiogram, x-ray, and physical examination, was by far the most serious part of the situation. The fatal issue emphasizes the importance of the



clinician's opinion against that of the surgeon's. A careful study had revealed slight but definite signs of heart disease, perhaps an old rheumatic aortic regurgitation and roughening or, more probably, arteriosclerotic aortitis with aortic regurgitation and the signs of early myocardial failure. The r-ray, but especially the electrocardiogram, corroborated the findings and indicated the extent and gravity of the myocardial lesion.

*Case VI—Acute Abdominal Pain After the Ingestion of Food or Drink in a Patient With Syphilitic Aortitis, Diffuse Aneurysm, and Aortic Regurgitation, With Relief of Pain After Two Weeks of Mixed Antiluetic Treatment*—A S., a laborer aged fifty-one, presented himself at the Charity Hospital Clinic because of stomach trouble. He complained of sharp pains in the pit of the stomach immediately after taking almost any kind of food or fluid, even soup and milk. Meat and beans produced severe cramps. He suffered no nausea and vomited only voluntarily to relieve his pain. He had to support his abdomen by the pressure of his hands when hurrying or going downstairs, otherwise he suffered pain and a sensation of "everything dropping out." He had never been jaundiced, but had been chronically constipated. The bowel movements had never been abnormal. His appetite had been good, but he had been afraid to eat. He had lost much weight. The patient attributed all his trouble to an accident seven years previous to admission when he was caught between a loaded hand truck and a post. His abdomen and chest were compressed and bruised, but the only lesion requiring attention was a contusion over the symphysis pubis, which broke down, suppurated, and had to be drained. His abdominal symptoms came on shortly after this. He had noticed slight dizziness and weakness at times. He had not experienced any dyspnea, palpitation, throbbing, or edema. His family history and marital history were negative except for the fact that his wife had a miscarriage in her first pregnancy. In his past history he had had no serious illnesses and denied having had any venereal infections.

The *physical examination* showed the pallor and sallowness of an aortic facies. There was a nodding of the head. The pupils reacted promptly to light and accommodation. The tongue was heavily coated. The carotids and subclavians throbbed vigorously. The aorta was not palpable in the suprasternal notch. A wave like pulsation was visible in the second right intercostal space. Vigorous epigastric pulsation was also noted. The superficial veins of the chest, axillæ, and arms were prominent. A vena corona costalis was also present. The heart was enlarged with the apex impulse extending 12 cm. to the left in the fifth interspace. The retromanubrial dullness was increased. A short aortic diastolic murmur was heard, transmitted poorly, but unchanged to the apex. There were also an aortic systolic and a mitral systolic murmur. The blood pressure was 110/40 in the brachials and 130/30 in the popliteals. A pistol shot sound and a diastolic Duroziez murmur were elicited in the compressed femoral artery. The tortuous

longitudinally pulsating brachials and radials were visible. The finger-tips throbbed and a capillary pulse was present.

The *abdomen* was scaphoid. Slight tenderness and resistance were elicited by pressure in the right side of the epigastrium. The liver edge was just palpable. The abdominal aorta's pulsations were dynamic.

The extremities were negative. No edema was present. The reflexes were active and equal. There was no loss of sense of motion or position.

The urine and blood studies, including the blood chemical examinations, revealed no abnormalities. The Wassermann was reported to be weakly positive.

The gastro-intestinal *x-ray* studies by Dr. Amedee Granger were entirely negative except for a slight irregularity of the duodenal bulb, which suggested the possibility of a chronic cholecystitis.

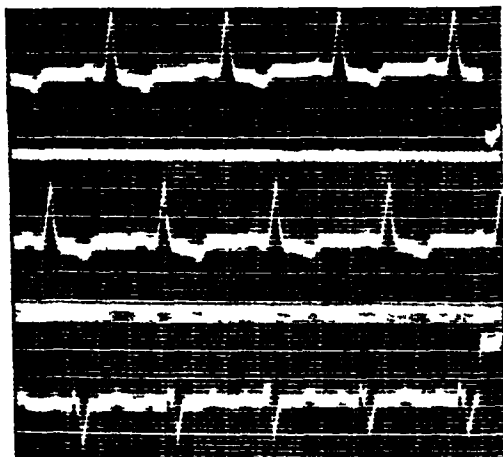


Fig 178—Case VI. Some left ventricular preponderance, negative I and III. Slightly broadened Q R S intervals (0.08 to 0.10 sec) and diphasic T waves with the L V P suggest slight incomplete block, defective intra-ventricular conduction in the right branch of the His bundle.

The *x-ray* of the heart revealed an aneurysmal dilatation of the aorta which measured 6.5 cm, while the heart shadow itself measured 14.5 cm in transverse diameter.

The *electrocardiogram* (Fig 178) shows a definite left ventricular preponderance with negative T waves in Leads I and II. The Q R S is slightly broad and this, with the diphasic T waves, suggests defective intra-ventricular conduction.

The patient was placed on mixed treatment consisting of six mercurial injections weekly and iodids by mouth, and within two weeks his gastric symptoms were entirely relieved. After six weeks a course of ten injections of bismuth salicylate (1.35 or 2 gr. each) was given.

*Discussion*—The case is quite definitely one of syphilitic aortitis, with diffuse aneurysmal dilatation and a free aortic regurgitation, without any of the symptoms that are usually present in such conditions, but with gastric symptoms that are really more frequent than one generally thinks. The gastrointestinal x-ray study was indecisive, but the heart x-ray and the electrocardiogram gave conclusive evidence of a grave cardiovascular lesion. The therapeutic test with mixed antiluetic treatment gave definitely positive results with relief of the pain within two weeks.

*Case VII—Psychic Disturbances in Attacks of Paroxysmal Auricular Fibrillation in a Patient Who Also Had Bundle Branch Block*—J. C. M., a bachelor, aged fifty-six, entered the hospital because of attacks of weakness, dizziness, and mental confusion. He had had attacks for eight years, but these for the most part had had to do more with shortness of breath and palpitation and some precordial radiating pain. Weak sensations, light headedness, and "a befuddled" mental confusion had been associated with the attacks for a year before admission. The onset of symptoms was always sudden, at most any time of the day, but especially in the evenings. The attack came on as often during rest as during heavy work. The drinking of cold water seemed to bring on the disturbance. The attacks with palpitation and pain had come on at intervals of a month, while the cerebral symptoms had come on as often as once a week for some weeks. When admitted, he was suffering from an attack which had persisted for two weeks without clearing up promptly, as the other attacks had.

His *past history* was significant in that he had been an excessive whisky drinker, consuming a quart a day for many years. He had had a "hard chancre," followed by skin and throat lesions, twenty years previous to admission. He had had numerous attacks of gonorrhea, the last of which was five years before admission. He had had mixed treatment with iodids and mercury for about five years. His family history was negative.

The *physical examination* showed a rather rough backwoodsman, who was at times disoriented. The eyeballs were prominent and this moderate exophthalmos gave the patient a slightly wild and anxious look. He was slightly cyanotic and dyspneic. The veins of the neck were engorged. The temporal arteries were thickened, tortuous, and rolled under the fingers. The brachials and radials were likewise thickened and tortuous and pulsation was visible and absolutely irregular.

The chest showed slight lagging at the right base. Absence of fremitus and resonance and the presence of distant breath sounds, egophony, and râles over the lower lobes of the lungs indicated hydrothorax. The breathing was Cheyne Stokes in type.

The *heart* was enlarged. The apex impulse was barely palpable behind the fifth rib, 11 cm. to the left of the midline. The whole precordium heaved

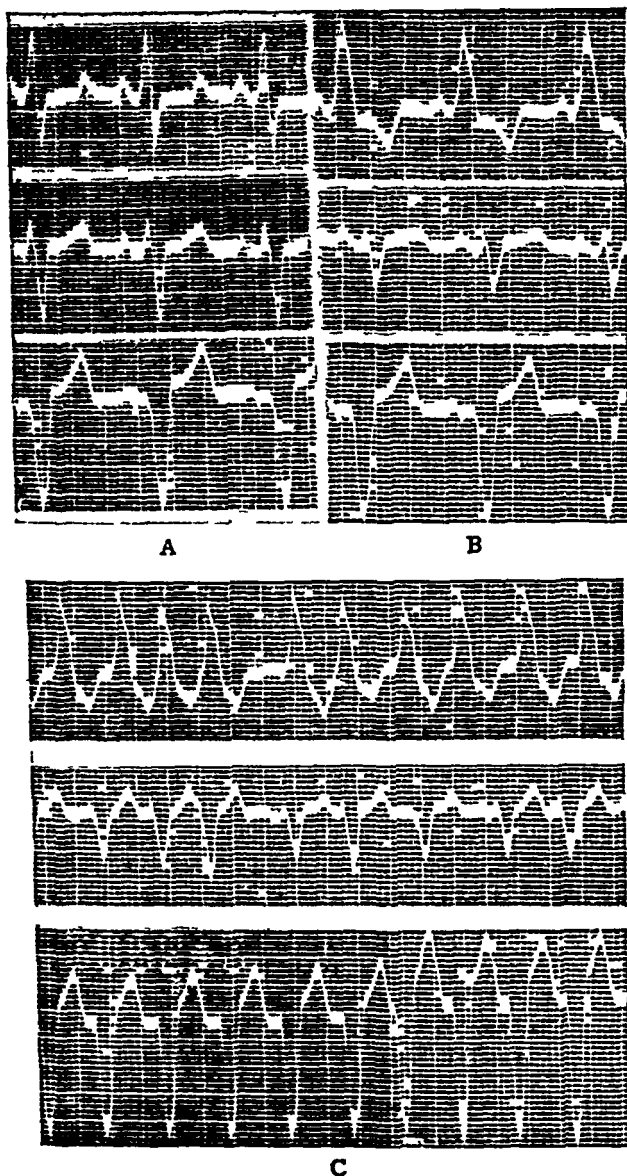


Fig 179 —Case VII A, High-grade incomplete bundle branch block. B, Complete right bundle branch block. C, Complete right bundle branch block combined with auricular fibrillation (paroxysmal)

with each systole and the right upper chest wall showed some abnormal systolic outward movement. No thrills or shocks were felt. The retromammary dullness was increased and the outer cardiac dullness extended 4 cm. to the right and 13 cm. to the left of the midline. The first heart sound was loud and the second was quite faint. Later the first sound became muffled. A rough blowing systolic murmur was heard at the apex and a soft systolic murmur was present in the aortic area. The cardiac rhythm was absolutely irregular and the rate was high, 160 per minute, while the radial rate was only 100. The blood-pressure was 170 to 190/100 to 110.

The abdomen was full. The liver edge was hard and not tender, and extended 6 cm. below the costal margin. The spleen was not palpable.

The extremities were negative except for edema about the ankles. The reflexes were normal.

The urine contained a faint trace of albumin and some hyaline casts. There were fairly well concentrated specimens, but a slightly increased night volume. The phthalein excretion totaled 50 per cent in two hours. The blood non-protein nitrogen was increased to 73 mg. per 100 c.c. The Wassermann was negative, even after provocative arsphenamin. The blood hemoglobin and counts were normal.

The x-ray of the heart showed enlargement, the shadow measuring 17 cm. transversely and 12.5 cm. longitudinally. The shadow of the great vessels measured 7 cm.

The *electrocardiograms* (Fig. 179, A, B, and C) were distinctly abnormal, showing defective intraventricular conduction, at first incomplete and later complete right bundle branch block. Auricular fibrillation was present at times, but normal mechanism most of the time, however.

During his stay in the hospital the patient's disorientation cleared up, but with the attacks of paroxysmal fibrillation he frequently suffered from mild delusions of persecution. Digitalis was given and had some effect on the longer periods of fibrillation, but the attacks recurred.

*Discussion*—The case is one in which psychic disturbances came on during attacks of paroxysmal auricular fibrillation. Other evidences of heart disease were present. Dyspnea, palpitation, cardiac pain with radiation into the arm, cyanosis, and edema gave evidence of a failing myocardium and the paroxysms caused still greater embarrassment and sufficient cerebral anemia to produce the psychic disturbances. The *electrocardiograms* revealed positive evidence of myocardial changes, of a severe nature, which singularly showed evidence of progression in the increase in the degree of bundle block while the patient was in the hospital. The combination of auricular fibrillation and defective intraventricular conduction gave quite unusual curves. We have had only a few more similar cases.

**Case VIII — *Psychic Disturbances in a Patient With a Free Luetic Aortic Regurgitation and Aortitis and Severe Heart Failure With Congestion and Massive Edema*** — A. T. H., a married man, aged forty-one, had been troubled by the beating noise in his head whenever he lay down at night, a faintness and "all gone" sensation on arising rapidly, and an increasing irritability, had some pain in the heart, right shoulder and neck, shortness of breath, and swelling of the feet. His illness dated back only six months, when he first noticed faintness and pain in the heart while at work. He continued doing heavy labor and his pain became progressively more severe and spread to his right shoulder and neck. Shortness of breath also became a prominent symptom. Within a few months he found that he could no longer do hard work, the faintness and weakness increased just as did the pain. Distress and pain in the abdomen began to trouble him and the swelling of the feet and legs was noted. He had a cough and expectorated blood at times. The beating noise in the head, the faintness and irritability had been constantly present for some weeks and were getting distinctly worse. Puffiness of the face appeared a week before he was admitted.

The past history was significant in that the patient had had a "hard chancre" twenty-five years previously and had received prompt local and mixed antiluetic treatment. No secondary lesions appeared. Two years later he had a mild sunstroke. His wife had had 5 children by a former marriage, but had not been impregnated by the patient in seven years of married life. The patient's father had died of cancer.

The *physical examination* showed puffiness about the eyes, slight dyspnea and cyanosis. The pupils did not react to light. The neck veins were engorged. Pulsations over the carotids and in the jugular fossæ were prominent. There was a nod of the head with every systole. The aortic arch was barely palpable in the suprasternal notch. No tracheal tug was noted.

The chest was large in all dimensions. There was slight lagging with absent fremitus, dullness to flatness on percussion, diminished breath sounds, egophony and bubbling râles at the bases of the lungs, especially on the right posteriorly.

The *heart* was enlarged. The whole precordium and upper chest heaved with each systole. The apex beat was visible in the fifth and sixth intercostal spaces extending to the anterior axillary line, that is, 19 cm. to the left of the midsternal line. No shock was felt. A definite diastolic thrill was felt over the left sternum from the second interspace to the apex. The outline of cardiac dullness measured 19 cm. to the left and 6 cm. to the right of the midline. The retromanubrial dullness was increased and measured 9 cm. across. The heart sounds were distant. A harsh, musical, aortic diastolic murmur was heard at the aortic cartilage and equally well along the left border of the sternum. The murmur was changed at the apex by the functional mitral stenosis to one of a rumbling character, an Austin-Flint murmur. Soft flowing systolic murmurs were heard at the base and at the apex.

A very marked water hammer pulse was noted. Loud systolic pistol shot sounds were heard in the brachial and femorals, posterior tibials and dorsalis pedis arteries. The sounds were louder on the right. The Duroziez

diastolic murmur was barely audible in the compressed femoral. Capillary pulsation and throbbing was present in the finger-tips. The blood-pressures were 180/50 in the right arm, 215/55 in the left arm, 265/75 in both legs.

The abdomen was distended. The liver was tender and enlarged, extending 6 cm below the costal margin. The spleen was not felt. A slight shifting dullness and fluid wave indicated some ascites. There was an old scar on the penis.

The extremities were edematous. The reflexes were not obtained. The peripheral blood vessels were tortuous and calcareous.

The urine contained albumin and many granular casts and leukocytes. The phthalein excretion was low, 27 per cent for two hours on one occasion,

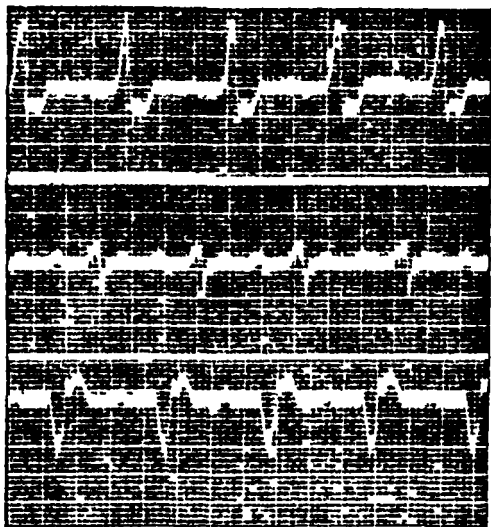


Fig. 180—Case VIII. Bizarre curves showing left ventricular preponderance, prolonged P-R (22 to 24 sec) and an increased Q, R, S (10 to 12 sec) and diphasic T waves (T negative). These signs indicate incomplete block in the right branch of the His bundle.

and 45 per cent on another. The blood showed a slight secondary anemia. The blood non-protein nitrogen level was 39 mg per 100 cc. The Wassermann was strongly positive.

The x-ray of the heart at 2 meters gave a shadow which measured transversely 22 cm and longitudinally 21 cm. The shadow of the great vessels measured 8 cm.

The electrocardiograms (Fig. 180) were distinctly abnormal. There was evidence of defective conduction in the His bundle and in its right branch. The P-R intervals measured from 0.20 to 0.28 sec, and the Q, R, S intervals from 0.08 to 0.11 sec. The T waves were diphasic and the signs of left ventricular preponderance were present.

The course in the hospital was a stormy one. Digitalis was administered without any conspicuous changes. The patient became quite irrational at nightfall and had mild delusions and hallucinations. He spat up blood occasionally and the heart failure increased rapidly. Pain in the liver region increased. His blood-pressure dropped 30 mm without improvement. He died five weeks after admission.

*Discussion*—The beating noise in the head, the faintness, and vertigo are easily accounted for by the very free aortic regurgitation and the consequent arterial throbbing. The other psychic disturbances are usually considered to be due to anemia in the special sense centers and general cerebral anemia in severe heart failure such as this patient presented.

*Case IX.—Asthma-like Attacks, Often Nocturnal, in an Individual With Arteriosclerotic, Possibly Syphilitic, Aortitis and Myocarditis and Evidence of Myocardial Insufficiency*—J. F., a widower, aged sixty-six, was admitted with the complaint of "asthma," which consisted of paroxysmal, especially nocturnal, attacks of tightness in the chest and difficulty in breathing. He had had one attack of this trouble fifteen years previously and none again until two years before coming to the hospital. At this time he was caught in a windstorm which brought on an attack of difficulty in breathing and a constriction sensation in the neck and the lower chest. He was not relieved until he was given a hypodermic injection. One more similar severe attack in the same year was relieved in the same way. He had no further trouble until about two months before admission, when he began to have similar attacks almost every night. The attacks were preceded by a sensation of heat and fulness in the head and were accompanied and followed by cough and a tenacious expectoration, which was bloody at times. The attacks were relieved by nothing but hypodermic injections. The nature of the drug which was used in these injections was not known, but it was presumed to be epinephrin. He suffered from a frequency during the day and nocturia four to five times each night.

The past history and mental history revealed no relevant facts. The family history was significant in that the patient's father and mother and one older brother had died of "asthma" and "heart trouble."

The *physical examination* showed an orthopneic old man with Cheyne-Stokes respiration, cyanosis of the lips, and engorgement of the neck veins.

The *chest* was somewhat barrel-shaped and the percussion note was tympanic except at the bases where slight dulness was noted and moist râles were heard.

The *heart* was enlarged; the apex impulse was in the sixth intercostal space and the forceful heave extended 12 cm to the left of the midsternal line. The retromamillary dulness was increased. The cardiac rhythm was regular. The first sound was somewhat muffled and a protodiastolic gallop rhythm was noted. A loud blowing systolic murmur replaced much of the first sound.



at the apex, and was well heard in the left axilla. The heart sounds at the base were only faintly audible. The blood-pressure was low on admission, but gradually rose to 155/100. The superficial arteries were thickened and slightly tortuous.

The *abdomen* was slightly distended. The liver was just palpable and definitely tender. The extremities showed clubbing of the fingers and toes. The feet, ankles, and legs were edematous. The reflexes were not abnormal.

The urine contained a trace of albumin, which, however, disappeared with rest. The specific gravity varied from 1007 to 1026. The phthalein

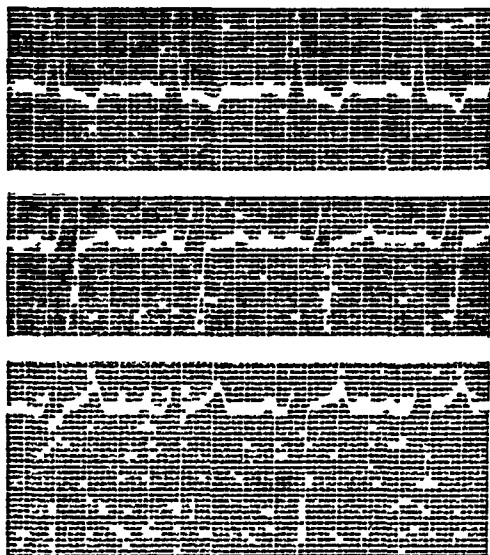


Fig 181—Case IX. Marked left ventricular preponderance, prolonged Q R S interval (12 sec) and diphasic T waves ( $T_1$  negative), indicating incomplete right bundle branch block.

excretion was 57 per cent for two hours. The blood-counts and hemoglobin content were normal. The Wassermann reaction was positive.

The *x-ray* of the chest at 2 meters showed the lungs to be clear, but the aorta and heart to be enlarged, with transverse diameters of 6.5 and 20 cm, respectively, and a length of 20 cm.

The *electrocardiograms* (Fig 181) were all distinctly abnormal, showing a very high grade of defective conduction, incomplete or almost complete block, in the right branch of the His bundle. The Q R S intervals measured 0.12 to 0.14 sec, with a very extreme degree of left ventricular preponderance, but with diphasic T waves. These findings were sufficient evidence of serious myocardial changes.

The patient remained in the hospital three weeks, during which time he was given rest in bed and digitalized and, as a result, he lost his edema and felt very much improved. The attacks of nocturnal dyspnea had ceased troubling him.

He fell dead a few days after leaving the hospital.

*Discussion*—The history was suggestive of an asthmatic bronchitis and the emphysema and râles at the bases may have been considered as supporting this diagnosis. The response to what was apparently epinephrin injections might have been thought of as corroboration by a therapeutic test. However, the evidence of a failing myocardium was abundant on physical examination and the x-ray and electrocardiograms substantiated this evidence and led to a diagnosis of cardiac rather than pulmonary disease. The improvement under treatment for myocardial insufficiency and his sudden exitus after leaving the hospital confirmed the diagnosis.

*Case X.—A Clinical Picture, Almost Typical of Asthmatic Bronchitis, Which Was Apparently the Result of Myocardial Insufficiency*—S B, a housewife, aged thirty-four, was admitted to the "asthma" clinic with the complaint of nocturnal wheezing in the chest, cough, and expectoration.

Her present illness was a continuation of attacks of paroxysmal difficulty in breathing that she has had for about two years. The attacks were usually nocturnal, coming on often in a "close" room, but occasionally also after exertion. Coughing, with shortness of breath, accompanied by some palpitation and lasting for two or three hours, with relief only after sitting up, was the usual sequence of events. Expectoration was profuse and at times blood tinged. Occasionally she had had cramps in the legs during the attack.

The family history was negative except for the fact that the patient's father was thought to have had "asthma," and one sister has had asthma. She had been married for fourteen years. She had no living children, but had had two miscarriages thirteen and twelve years back. Her husband was well.

In her past history she had had no acute infections. In November, 1918, she had had influenza, which had begun with a cough and with "whooping," as in pertussis. She had coughed all that winter, but not during the following summer (1919). In the fall of 1919 the cough and frequent expectoration began with the onset of cool weather and became worse until the warm weather of the spring of 1920. Occasionally thick gray sputum was expectorated after the attacks.

The *physical examination* showed a moderately orthopneic woman, slightly cyanosed and definitely in distress. The neck veins were slightly

engorged. The chest was slightly hyperresonant and moist râles were present at the bases of both lungs.

The heart was enlarged, extending 12 cm. to left and 4 cm. to right of the midsternal line, by percussion. The point of maximum impulse was in the sixth intercostal space 10 cm. to the left of the midsternal line. The pulmonary second sound was louder than the aortic second sound, with a suggestion of reduplication. The mitral first sound was muffled and a faint blowing systolic murmur was heard at the apex, but it was not transmitted. The systolic blood pressure was 190 mm. of mercury and the diastolic was 110 mm.

The abdomen was negative. The liver and spleen were not palpable. There was no tenderness. The extremities showed only slight cyanosis and edema. The urine contained a very slight trace of albumin, a few hyaline

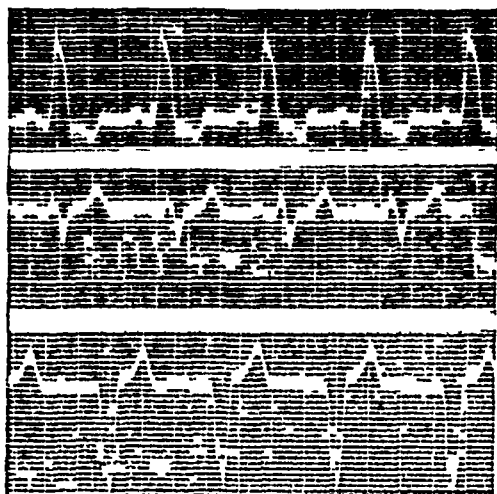


Fig. 182—Case X. Complete right bundle branch block,  $P_2$  negative.

casts, and a few leukocytes. The blood examinations revealed no abnormality and no eosinophilia. The Wassermann was negative. The sputum was negative. The sensitization tests were negative.

The x-ray of the chest taken at 2 meters showed no evidences of gross pulmonary pathology. The heart was enlarged, with a transverse diameter of 14 cm., while the shadow of the great vessels measured 6 cm. in width.

The electrocardiograms (Fig. 182) were the most convincing bit of evidence as to the source of the patient's difficulties. The curves showed a very broad Q-R-S interval (12 to 14 sec.), with a broad notching and diphasic T wave, the signs of defective conduction (complete block) in the right branch of the His bundle. These findings were definite evidence of myocarditis.

The patient was kept in bed on a low protein salt poor diet and given tincture of digitalis in tonic doses. Two crowned teeth that were abscessed

were removed. Her symptoms were markedly relieved and her blood-pressure dropped to 155/95, but later rose to 185/125, but attacks were no longer troublesome.

*Discussion*—Though the patient's story and symptoms were those of an asthmatic bronchitis, the physical, x-ray, and electrocardiographic findings definitely established the presence of grave myocardial changes. The relief of symptoms under cardiac treatment may be taken as confirmative evidence that heart disease was at the bottom of this patient's trouble, as it is in many cases of so-called bronchitis and asthma.

*Case XL—4 Case Presenting a History and an Appearance of Laryngeal or Tracheal Obstruction, the Result of an Aneurysm of the Innominate Artery*—O R P, a widower, aged forty-five, came to the hospital because of obstruction to breathing, hoarseness, loss of voice, rattling in his windpipe, stridor, wheezing, a dry cough, and tightness in the upper right chest. The trouble had begun eight months previous to admission with a "cold," a sensation of tightness in the right upper chest, and an unproductive cough. He had not aspirated any foreign body as far as he knew. Hoarseness and difficulty in speaking had been noticed for about four months. Acute "paroxysmal" attacks of difficulty in breathing had been coming on irregularly for three months. The attacks had been cut short by the smoking of "asthma powders." After the attack a "rattling" and "wheezing" and a sense of "closing off of the windpipe" persisted. He had been suffering from an acute attack for six days previous to admission.

The family history was irrelevant, but the marital history was of some interest, in that his wife had never become pregnant and had died of "kidney trouble." In his past he had had gonorrhea at fourteen years, but denied having had any soft or hard chancres. He had had influenza in 1918, and frequent "colds on the lungs each winter."

The *physical examination* showed a middle-aged man in evident respiratory distress. A distinct inspiratory stridor and an expiratory wheezing were audible without a stethoscope. The voice was weak and hoarse and the cough somewhat "brassy." There was considerable throbbing and questionably expansile pulsation in the right supraclavicular space. The neck veins were engorged. A tugging of the trachea was also felt. The right sternoclavicular joint, manubrium, and upper chest were raised with each heart beat. Systolic and diastolic shocks were felt over this area. The apex impulse was in the fifth interspace, 10 cm to the left of the midline. The retromanubrial dullness measured 10.5 cm and the outer cardiac dullness extended 4 cm to the right and 10 cm to the left of the midsternal line. The heart sounds were distinct and normal, no murmurs were heard. The sounds were well heard over the upper right chest also.

The chest showed dullness at the right apex. Sonorous, piping, squeaking, and whistling sounds were heard over the lungs posteriorly.

6 cm to the left of the midsternal line. A slight heave and a faint diastolic shock were felt over this dull area. A loud, long aortic diastolic murmur was most audible in the aortic area in the second right intercostal space near the sternum. The aortic diastolic murmur was not transmitted to the secondary aortic area and the apex. A loud apical systolic murmur was heard at the apex and well transmitted to the axilla. The rhythm was regular. The heart sounds were obscured by the murmurs. The blood pressure was 144/80 in the right arm and 130/80 in the left arm.

The extremities were negative except for hippocratic finger nails and slight clubbing. The radial pulses were about equal and not of a collapsing type.

The urine was negative. The blood was numerically, colorimetrically, and morphologically negative. The Wassermann was positive.

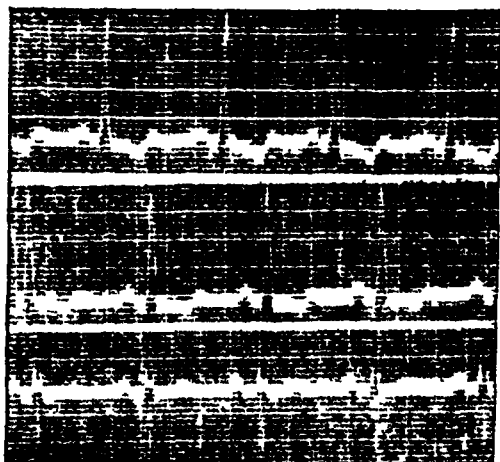


Fig. 184—Case XII. Definite left ventricular preponderance  $T_1$  and  $T_2$  negative, T waves diphasic, Q-R-S interval at upper limit of normal (0.08 sec). Findings suggestive of slight defective conduction in the right branch of the His bundle.

The x-ray of the chest showed a greater clearness of the right lung field than of the left. The heart and great vessels appeared drawn to the left. There was a diffuse mottling in the left upper lobe. A dense rounded shadow measuring 15 cm. across filled the mediastinum and extended into the left lung field from the second to the fourth ribs. The mass did not pulsate, the left diaphragm was very limited in its movements. The heart shadow extended 5.5 cm. to the right and 9.7 cm. to the left of the midsternal line. The lung field findings suggested tuberculosis or possibly pressure occlusion of the left primary bronchus with atelectasis and possibly secondary infection.

The mediastinal mass from the x-ray standpoint was considered to be a solid tumor, probably malignant.

The *electrocardiogram* (Fig 184) showed definite left ventricular preponderance and negative T waves in Leads I and II. The Q R S interval was at the upper limit of normal (0.08 sec.) and the diphasic T waves suggest slight defective conduction in the right branch of the His bundle.

The patient failed to respond to mixed antiluetic therapy and gradually lost ground. He had a persistent low-grade fever which gradually became higher and assumed a septic character. A leukocytosis of slight degree was present. Difficulty in breathing increased and cough and expectoration was uncontrollable.

Autopsy showed an aneurysm of the root transverse arch and descending portion of the aorta. The left superior bronchus was obstructed and the atelectatic left upper lung lobe was infected and the bronchi filled with purulent material.

*Discussion*—The case is interesting from many angles. There were symptoms and signs that might well indicate an apical tuberculosis. The evidences of aneurysm were found on careful examination and the inferred obstruction of the primary bronchus suggested by the x-ray was confirmed at autopsy. The atelectasis and secondary infection explained the findings, including the fever. The reason for the non-transmission of the loud aortic diastolic murmur and the absence of the secondary findings of aortic insufficiency lay probably in the presence of a sacculatation at the root of the aorta, which was responsible for much of the murmur and acted as a blood-trap.

*Case XIII.—The Symptoms and Signs of Pulmonary Tuberculosis in a Patient With Advanced Mitral Stenosis and Passive Congestion of the Lungs, With a History Also of Pulmonary Thrombosis, Cerebral Embolism With Hemiplegia, Cough, Hoarseness, Aphonia, and Cardiac Pain*—M. M. E., a widow, aged twenty-seven, came into the hospital because of weakness, cough, blood-tinged sputum, pain in the chest, and some loss of weight. The symptoms had been more or less insidious in onset and had developed gradually over a period of years. Fever had been present irregularly and her appetite had failed in the febrile periods.

Her past history was replete with significant happenings. She had had repeated attacks of severe sore throat and quinsy since childhood, but without any rheumatic fever or chorea. Attacks of stomach trouble with slight cramping for fifteen minutes after taking most any kind of food had been noted off and on for many years. She had had frequent severe colds during each winter. Two years before admission she was suddenly seized with a pain in the right back, this was followed by shortness of breath, cough, and bloody sputum. A diagnosis of pneumonia had been made. (The condition was most probably, however, a pulmonary infarction.) A few months later

the patient had an acute pain in the right side of the head. This was followed by a paralysis of the left side of the body.

Occasionally after a severe paroxysm of coughing she suffered from a sharp pain in the precordium, which radiates to the left shoulder and down the left arm and was accompanied by a choking sensation, severe shortness of breath, palpitation, and dizziness. Her voice was often hoarse and at times she was almost aphonic.

The *physical examination* showed a woman of slight build with an anxious expression and a flush over the malar prominences. There was a slight tinge of cyanosis of the mucous membranes. The tonsils had been removed. The neck veins were moderately engorged. The thyroid was slightly enlarged.

There was some impairment of percussion at the left apex and at the bases. The vocal fremitus was slightly increased at the left apex. The breath sounds were bronchovesicular and a few fine râles were heard at the left apex. Diminished fremitus, muffled breath sounds, and coarse râles were present at the bases posteriorly.

The *heart* was enlarged, the apex impulse was visible in the sixth intercostal space 14 cm. to the left of the midsternal line. A diastolic thrill was felt over the apex and a diastolic shock over the pulmonary area. The dulness at the base was distinctly increased to the left. The first sound at the apex and the pulmonary second sound were sharply accentuated. The aortic and mitral second sounds were quite faint. A localized rumbling diastolic and a loud widely transmitted systolic murmur were heard at the apex. The heart rhythm was regular. The blood-pressure was 90/65. The pulse was small.

The abdomen was slightly distended and tense. The liver was engorged and tender, extending down to the level of the umbilicus. The spleen was also palpable.

The extremities showed a paralysis of the left side. The reflexes were exaggerated on the left. A Babinski and a patellar clonus were present in the flaccid, cold left leg. There was a slight edema of the pretibial tissue.

The patient's best weight had been 110 pounds. Her weight on admission was 94 pounds.

The urine contained a trace of albumin and some hyaline and granular casts. The phthalein excretion was 50 per cent in two hours. The blood showed a slight polycythemia and a slight leukocytosis. The blood non-protein nitrogen level was normal and the Wassermann was negative. The sputum was repeatedly negative for tubercle bacilli.

The *x-ray* showed slight haziness at the left apex and at the bases of the lungs. The bronchovascular tree was prominent throughout. The heart was greatly enlarged, the shadow measuring 4 cm. to the right, and 15 cm. to the left of the midsternal line. The shadow of the left auricle was also very prominent.

The electrocardiogram (Fig. 185) showed prominent, broad P waves and the evidence of a right ventricular preponderance, which together are pathognomonic of a high-grade mitral stenosis. The Q R S interval was slightly broadened, suggesting myocardial lesions involving the intraventricular conduction tissue.

The patient did fairly well under treatment for her heart condition. The slight fever promptly disappeared with rest in bed and digitalis. She went home, but was brought back three months later, in the early winter, with a complicating acute respiratory infection which terminated in a fatal bronchopneumonia.

Autopsy showed a bronchopneumonia due to pneumococci of Group IV. There were no evidences of tuberculosis. The right heart was greatly enlarged. The left auricle was greatly dilated and contained a mural thrombus. The mural valve was stenosed and admitted only the tip of the finger. The

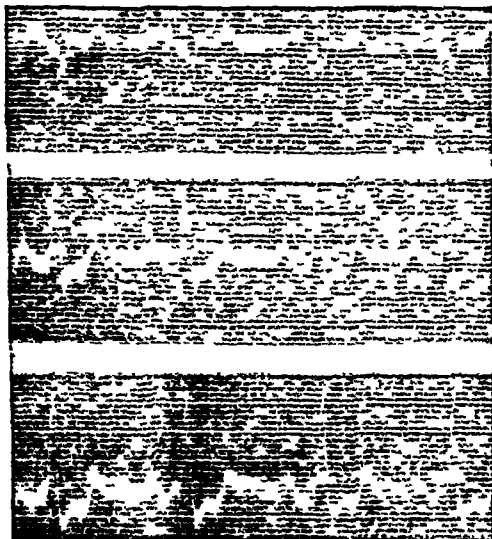


Fig 185—Case XIII. Right ventricular preponderance, prominent broad notched P waves especially in Lead I. Q R S interval prolonged (10 sec. time marker in tenths and fiftieths). There is a suggestion of slight defective intraventricular conduction most probably in the left branch of the His bundle.

tricuspid and aortic valves also showed old scars. The liver and spleen were enlarged due to chronic passive congestion.

*Discussion*—This case is an interesting one, presenting many unusual features. The symptoms and signs of pulmonary tuberculosis were quite prominent on admission and were evidently the result of the pressure of the engorged left auricle and the extreme passive congestion of the lungs. The pulmonary infarction, which had been diagnosed pneumonia, was evidently



the result of stasis of the blood in the veins and a resulting thrombosis. The predisposition to colds was also the result of pulmonary congestion. The abdominal symptoms were probably associated with the engorged liver. The cough, hoarseness, and aphonia were the results of the pinching of the left recurrent laryngeal nerve between the aorta and the dilated pulmonary artery.

The attacks of cardiac pain that came on after severe paroxysms of coughing and simulated "angina pectoris" attacks may be accounted for by the pressure of the engorged left auricle on the left coronary artery, with a resulting narrowing and temporary occlusion.

The acute headache and subsequent hemiplegia were the results of a breaking off of a bit of the auricular thrombus and cerebral embolism.

The electrocardiogram in this case was of the type characteristic of mitral stenosis and in itself would have pointed to the correct diagnosis.

*Case XIV — Hemoptysis and Cough, for Which the Patient Had Been in a Tuberculosis Sanatorium, While the Real Cause of the Trouble Was a Congenitally Defective Interventricular Septum With an Active Congestion of the Lungs*—M. H., a school-teacher, came to the clinic because of a chronic cough and the expectoration of various amounts of bloody sputum. He had been having some slight difficulty for about two years. Blood streaked sputum was noticed in slight amount at first only after a severe paroxysm of coughing and then after severe muscular effort. The patient, however, was not "short-winded", on the contrary, he was exceptionally "long-winded" and could swim long distances. He had noticed no conspicuous loss of weight and had had no fever that he could detect without a thermometer. His appetite had not been good, but no serious falling off had occurred. He had been sent to a tuberculosis sanatorium, where he had taken the treatment for a number of months, but the symptoms did not completely disappear even with absolute rest.

His *past history*, as originally given, was quite irrelevant. There was no knowledge of any exposure to tuberculosis. The family and marital histories were negative.

The *physical examination* revealed a thin, tall man of an asthenic habitus with an adenoid facies. The mouth and pharynx were negative. The teeth and gums were normal and the tonsils had been removed. The chest showed a slight precordial bulging, but the movements of the thoracic cage were symmetrical. The percussion note was slightly impaired over both lungs. The fremitus was slightly increased. The breath sounds were likewise bron-

chovesicular The whispered voice was unusually widely transmitted A few crepitant râles were heard throughout the lungs, especially at the apices and bases

The heart was greatly enlarged and extended into the axilla The apex impulse was visible in the fifth intercostal space 16 cm. to the left of the midsternal line A long systolic thrill was felt over the base of the sternum and up as high as the third rib and laterally for a few centimeters on either side of the lower half of the sternum A loud, rough systolic murmur was heard with maximum intensity over this same area The pulmonary second sound was distinctly accentuated The blood-pressure was low, 100/60

The abdomen was negative The liver and spleen were not palpable. The extremities showed no abnormalities There was no clubbing, although there were hypocratic nails The reflexes were normal

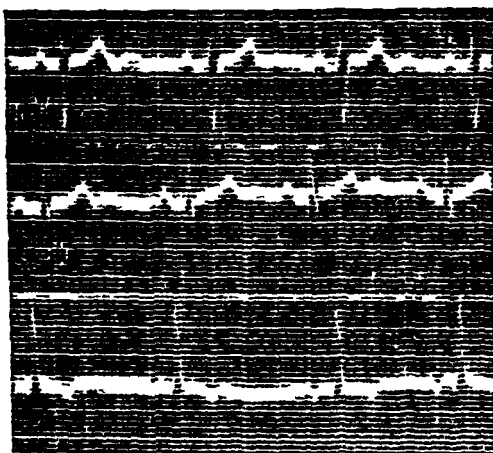


Fig 186—Case XIV Conspicuous right ventricular preponderance such as one encounters in congenital heart disease,  $P_2$  and  $T_2$  negative

The sputum was repeatedly negative for tubercle bacilli The urine was negative The blood-counts and hemoglobin content were slightly above normal The Wassermann was negative

The electrocardiogram (Fig 186) showed a very marked right ventricular preponderance such as is found only in congenital heart disease Thus the diagnosis of a congenitally defective interventricular septum was substantiated

The x-ray studies showed an enlarged heart, with a dilated, conspicuously pulsating pulmonary artery, the pulsations extending far out into the broncho-vascular tree The cardiac shadow on the film measured 4 cm. to the right and 16 cm. to the left of the midsternal line The transverse diameter of the shadow of the great vessels was 7.5 cm., much of the increase being due to a prominent pulmonary artery The x-ray findings were those of a congenital heart lesion and strongly suggested the presence of a patent ductus arteriosus

(Botalli) However, this could not be confirmed by careful auscultation, as only the evidences of a defective interventricular septum could be found

*Discussion* —The symptoms and signs that suggested pulmonary tuberculosis in this patient were not by any means sufficient for a diagnosis, yet the patient had been treated in a sanatorium. Of 4 cases of apparently more or less uncomplicated defective interventricular septum, only 2 had had hemoptysis and cough, while the other 2 were without any symptoms whatever. The diagnoses were based on the position and transmission of the thrill and the systolic murmur. The patient's past history was negative, but, on further quizzing after the above findings, he and one of the other cases recalled the important fact that his mother had told him that he had been a "blue baby" and had not been expected to live for a number of days after birth. The *electrocardiograms* furnished valuable confirmatory evidence and in themselves were diagnostic of congenital heart disease. The x-ray findings were likewise those of congenital heart disease. The final opinion, however, as to the type of lesion present rested upon the findings elicited by careful physical examination, especially palpation and auscultation.

*Case XV —A Patient With Paroxysmal Auricular Fibrillation and the Clinical Picture of Intestinal Obstruction, No Evidence of Which Could Be Found at Operation or Autopsy. Paroxysmal Auricular Fibrillation Was Finally Agreed Upon as the Most Logical Etiologic Factor* —C. P., a bachelor, aged sixty-four, was admitted as a surgical emergency because of acute pain in the abdomen, nausea, and constipation. The pain had begun two days before admission, but had been severe for only six hours. A dull constant pain had been present and acute exaggerations had occurred at irregular intervals, coming on more and more frequently, until they occurred every two or three minutes and lasted from fifteen to forty-five seconds. With the acute pain there was a drawing up of the knees close to the abdomen and convulsive movements and a congestion or suffusion of the face. The patient groined and complained of pain. He felt nauseated, but did not vomit. He had not had a bowel movement for two days.

The *past history* was considered negative, yet it was later learned that the patient had had recurrent attacks of severe abdominal pain for at least four years.

The *physical examination* revealed a pinched expression. There were evidences of paroxysms of excruciating abdominal pain. The left pupil was larger than the right, irregular, eccentric, and reacted poorly to light and

accommodation. The left eye had been traumatized and the abnormalities were probably the results of synechiæ. The neck vessels were slightly engorged and pulsated irregularly at times.

The chest moved symmetrically with each respiration. Slight orthopnea was noted and the respiratory rate was slightly increased up to 26 per minute. The lungs were resonant and clear throughout. The heart was at the upper limit of normal in size. Moderate accentuation of the aortic second sound was noted along with slightly rough systolic murmurs at the base and apex. The rhythm was regular at 84 beats per minute with periods of irregularity and more rapid rhythm. The blood-pressure was 145/85. The brachial and radial arteries were thick and tortuous. The pulses were full and bounding, regular, with short periods of irregularity.

The abdomen was distended, tympanitic, very tense and rigid in attacks and moderately so between attacks. Generalized tenderness was present, and besides the rigidity a vague mass was palpable in the right upper quadrant. Peristalsis was visible in the upper abdomen moving downward.

The extremities showed no edema. The reflexes were slightly reduced, but not abnormal.

The urine was negative. The leukocyte count was normal, 8000. There was only a very slight rise in temperature to 99° F.

The surgeons considered intestinal obstruction the most likely diagnosis. The patient was given morphin, 10 mg (1/6 gr), and atropin, 0.3 mg (1/150 gr), and operated under gas, oxygen, and ether anesthesia. No intestinal obstruction or volvulus was found. The bowel was greatly distended with gas. A moderate amount of free fluid was present. The mesocolon was thick with edema. No peritonitis was present. There was a small splenic hemorrhage and many congested areas.

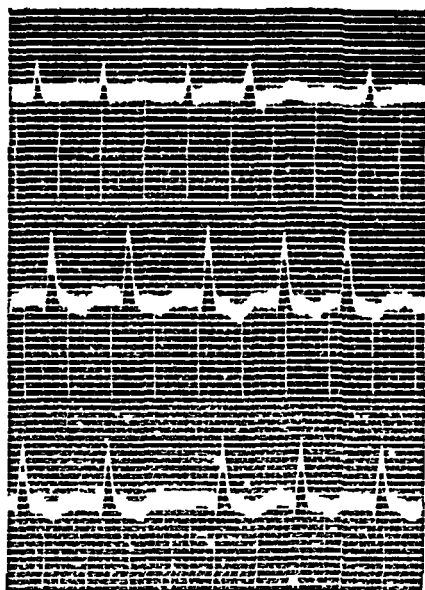
The patient rallied after the operation, but after eighteen hours the pulse was noted to be more constantly irregular and very weak. The blood-pressure was 90/60. The leukocyte count dropped to 5200. The respirations rose to 30 per minute. The temperature rose to 102° F. The bowels moved following an enema. After twenty-four hours postoperative the chest filled up with râles and the breath sounds were obscure. The patient became cyanotic and went into a state of collapse. The pulse was regular at times, but mostly irregular and rapid. At the end of forty-eight hours postoperative signs of consolidation were found in both lungs. The fever rose to 104° F, the pulse to 110, and the respiration to 40. The pulse was quite irregular most of the time, and *electrocardiograms* (Fig 187, A, B) showed this irregularity to be due to a high-grade auricular fibrillation. Electrocardiograms showing normal mechanism were also obtained.

The patient lost ground rapidly and died on the third day after operation.

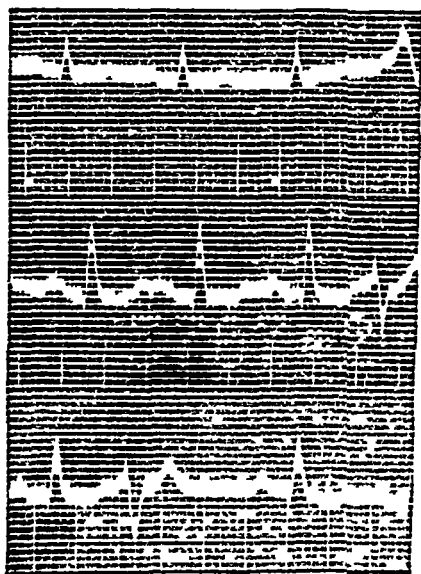
The autopsy showed a bilateral lobar pneumonia, bilateral hydronephrosis, dilatation of the ureters, bladder, and urethra (the so-called neurogenic G U syndrome), chronic interstitial orchitis, multiple hemorrhages into the peritoneum, acute swelling of the spleen, and chronic swelling of all viscera.

The heart was enlarged and fatty. The aorta and coronary arteries were thickened and slightly tortuous. The myocardium showed evidences of fatty and pigment degeneration. The aortic and mitral valves were





A



B

Fig 187—Case XV A, Auricular fibrillation of high grade (paroxysmal)  
B, Normal mechanism with left ventricular extrasystoles

slightly thickened    Fibroblastic proliferation was in evidence throughout the myocardium

*Discussion*—The patient presented the picture of an acute abdominal condition, but the subsequent course disproved this contention. It is clear that the patient was suffering from attacks of paroxysmal auricular fibrillation and also has some coronary disease. Either one of these disturbances has been known to account for clinical pictures similar to that which the patient presented. Certainly the combination of the two conditions would give adequate reason for the symptoms. However, there are two other possibilities. The eye findings along with the genito-urinary findings suggest neural syphilis with tabetic crises as the cause, while the lobar pneumonia may not have been secondary to the etherization, as it was considered, but may have been basal and central and involved the diaphragmatic pleura, which would have accounted for the pain. The T P R curve was, however, against this. Then, too, the past history of previous attacks made the first two explanations more plausible than the third. The history of the eye trauma to explain the findings makes the possibility of a tabetic crisis less likely than the first explanation, of paroxysmal auricular fibrillation and coronary disease, for which we have clinical and postmortem evidence.

*Case XVI.—A Patient With Heart block and Adams-Stokes Attacks Developed Symptoms and Signs of Acute Appendicitis, for Which He Was Operated. The Appendix Was Scarcely Badly Enough Involved to Account for the Symptoms and Signs*—W. R., a retired merchant aged seventy-two, was admitted as a surgical emergency with the complaint of acute pain in the right side of the abdomen, nausea, and vomiting. The onset of his pain had been sudden, just after a moderately heavy meal on the day previous. The pain was sharp and more or less generalized at first, but later more definitely right sided. Nausea and vomiting were noticed shortly after the onset of the pain. He was brought into the hospital in an ambulance. It was found that he had a few degrees of fever and a leukocytosis, along with a continuation of the abdominal pain, tenderness, and rigidity. He was consequently sent to the surgical service.

The *physical examination* showed an old man in evident distress and slightly cyanosed. The neck veins were slightly engorged. The chest was barrel shaped. The lungs were emphysematous with a few atelectatic and

chronic bronchitic râles at the bases posteriorly. The heart apex and borders could not be made out because of the pulmonary emphysema. The heart sounds were faint, the rhythm was slightly irregular, and the rate (72) was slightly less than might be expected in the presence of a body temperature of  $101^{\circ}\text{F}$ . The systolic blood-pressure was slightly elevated to 155 mm and the diastolic somewhat lowered to 70 mm of mercury. The abdomen was distended and extreme tenderness was elicited by slight pressure over the right side. The right rectus was distinctly rigid. No masses could be made out. Rectal examination was negative. The extremities were negative. There was a moderate leukocytosis of 15,000, 65 per cent of which were neutrophilic polymorphonuclears.

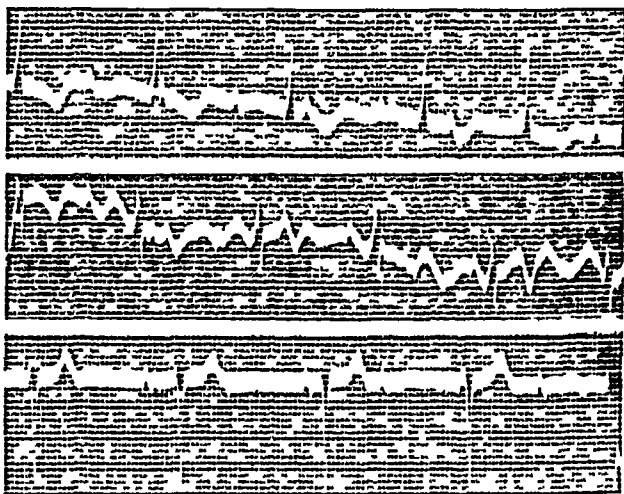


Fig 188—Case XVI. Heart block, for the most part complete A-V dissociation. At times there was partial 2 to 1 block.

The patient was operated for an acute appendicitis, but the appendix was admittedly not as seriously involved as the symptoms had indicated. The patient developed an increasing pulmonary edema, a bronchopneumonia, and died on the fourth day after operation.

Although this may have been a patient suffering from an appendicitis, there is, in my opinion, more evidence to suggest that his acute abdominal symptoms were due to acute disturbances in the cardiac mechanism. He had been previously operated for acute bladder symptoms. Just as the prostate was removed the patient collapsed, became unconscious and cyanotic, his body became rigid, and respiration practically ceased during a convulsion. No pulse was felt and adrenalin was administered. A lone beat was felt shortly after the injection, and a few seconds later the rate began to pick up and promptly rose to 40. Atropin was given to a total of 0.00658, or  $1/10$ .

gr The rate steadily increased after this to 80 and later 96 beats per minute. A diffuse flush and a dryness of the mucous membranes, the result of the heavy atropin dosage, were only slightly disturbing. The patient's brother had also had Adams-Stokes attacks and had died in an attack.

*Electrocardiograms* (Fig 188) showed various stages of heart-block, from merely delayed A V conduction and low-grade block to complete heart-block.

*Discussion*—The evidence is not sufficient to make the case a clear-cut one of Adams-Stokes attacks with abdominal symptoms. However, there is enough data at hand to make such a diagnosis highly probable. The case, nevertheless, serves to call attention again to the fact that heart-block cases may present the clinical picture of an acute surgical condition in the abdomen. The slowness of the pulse should arouse the consultant immediately to suspect the cardiovascular system and to study the case carefully from this point of view. Whenever possible an electrocardiographic study should be made, for this may reveal changes in conduction that are most difficult to detect by our senses of hearing and touch. The early stages of auriculo-ventricular block, where there is merely an increased A V conduction time and the presence of incomplete or complete bundle branch block, can be detected only in the electrocardiogram.

*Case XVII.—Subacute Bacterial Endocarditis Presenting the Picture of a Severe Nephritis With Uremia*—L. H., a housewife aged thirty-six, was brought into the hospital because of headache, drowsiness, failing vision, weakness, loss of appetite and color, puffiness of the face, frequency of urination at night, and some shortness of breath.

The patient's story was obtained with difficulty. The onset of her trouble had been very insidious. She had had her fourth child about a year previous to admission and her trouble came on shortly after this, when she noted fever, slight chills, and headache. The symptoms progressed rather rapidly from the very onset. Frequent nosebleeds were a source of much worry at first. The headaches became quite severe and were somewhat relieved by the nosebleeds. Weakness, pallor, puffiness of the face, and shortness of breath appeared in rather rapid succession and gradually increased in severity. She had lost her appetite for food about ten months before coming to the hospital. She had not lost much weight and had "swollen up" all over her body. Her eyesight gradually failed her until everything looked blurred. She had had to get up several times a night for many months. She had been unable to do her housework for several weeks. Her past history and family history contained no relevant facts.

The *physical examination* revealed a woman of large frame, but flabby musculature. She was pale and pasty with puffiness about the eyes. A



definite drowsiness was evident, but the patient could be aroused without much difficulty. An occasional muscular twitching was noted. The neck veins were not engorged.

The percussion note was impaired over the lung bases, the breath sounds were distant in the areas of dullness, and many bubbling râles were heard in the lower lobes of the lungs, indicating some edema and hydrothorax.

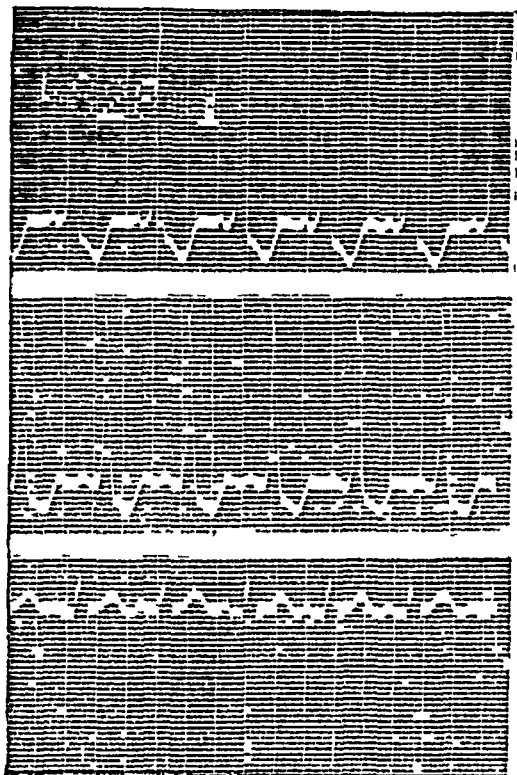


Fig 189—Case XVII. Most conspicuous left ventricular preponderance. Q R S interval increased (10 sec).  $T_1$  and  $T_2$  negative and all T waves diphasic indicate incomplete right bundle branch block.

The heart was somewhat enlarged. The apex impulse was found in the fifth intercostal space 13.5 cm to the left of the midsternal line. No thrills or shocks were felt. The aortic second sound was accentuated, and the pulmonary second sound was also loud. The mitral first sound was muffled. A loud, slightly rough, systolic murmur was heard at the apex and transmitted to the axilla. A questionable, short, rumbling diastolic murmur

was heard at times. The heart rhythm was regular and the rate was increased to 110 per minute. The blood-pressure was 220/110.

The abdomen was distended. The liver was tender and enlarged and extended 6 cm. below the costal margin. The spleen was slightly enlarged and palpable. There was edema of the abdominal wall and back.

The extremities were edematous. No petechiæ were present. The reflexes were not abnormal.

The urine contained albumin, a few hyaline and finely granular casts, leukocytes, and erythrocytes. The specific gravity did not rise above 1.015 and the day and night volumes were increased and about equal. No phthalein was excreted in the two-hour test period. The blood showed a severe secondary anemia. The Wassermann was negative. The non-protein nitrogen content varied from 145 to 185 mg. per 100 c.c., while the uric acid content averaged 16 mg. and the creatinin ranged from 5 to 7.2 mg. per 100 c.c. The blood-cultures repeatedly showed a non-hemolytic green-producing streptococcus. Only on two occasions was fever noted, and then only a degree and a half was the maximum increase.

The blood-pressure rose to 265/130, and the twitchings and drowsiness increased, but were relieved temporarily by intravenous injections of glucose solution.

The x-ray of the heart taken at 2 meters showed enlargement. The transverse diameter measuring 21 cm. and the longitudinal diameter measuring the same. The shadow of the great vessels measured 5 cm.

The *electrocardiograms* (Fig. 189) were conspicuously abnormal. They showed an extreme degree of left ventricular preponderance, diphasic and prominent T waves, and a slight increase in the width of the Q-R-S, indicating some defective conduction (incomplete block) in the right branch of the His bundle. The patient left the hospital against advice and died within a week after her discharge.

**Discussion**—The predominating symptoms and signs were those of a subacute nephritis with uremia, but the history of the onset following pregnancy, with fever and slight chills, the rapid progress, the cardiac and electrocardiographic findings, the enlarged spleen and the hematuria, along with the positive blood-cultures, are enough to warrant the diagnosis of a subacute bacterial endocarditis as the primary condition. I have seen 2 similar cases in males who came to autopsy and were thus proved cases of endocarditis masquerading as nephritis and uremia.

**Case XVIII.**—*Subacute Bacterial Endocarditis With Most Protean Manifestations Simulating a Blood Dyscrasia, Malaria, Kidney Stone and Nephritis, Chronic Pulmonary Tuberculosis, Cerebral Lesions, and Chronic Gastritis*—D. C., an unmarried laborer aged twenty-seven, came to the hospital complaining of general weakness, loss of color, weight, and appetite, chills and

fever, night-sweats, constant dull pain in the abdomen with occasional sharp pains in the left upper abdomen and both flanks, pains in the joints, epistaxis, and hematuria

The patient's trouble had begun very insidiously about a year before admission with general weakness, which forced him to give up his heavy work as a section-hand. Pallor was also noted at this time and his condition was considered to be due to "thin blood." The weakness gradually increased, the patient lost his appetite, and began losing weight. He lost 28 pounds within a year. He had been troubled some by an unproductive cough.

For about three months he had had severe chills, true rigors each morning, with high fever subsequently. Drenching night-sweats had also been troublesome. Quinin treatment had not proved effective. He had to give up all work at this time. Palpitation and dyspnea had been noted after exertion. He had suffered from occasional sudden sharp pains in the flanks and especially in the left side of the abdomen. Frequency and nocturia were present and the urine had often been red. Sudden sharp pains in the left side of the head, with some vertigo, mental clouding, and confusion had also been noted. Oozing nosebleeds and frequent bleeding of the gums had often been difficult to stop. He had had crops of reddish-purple spots over his shoulders and legs. He had had dull aches in the joints for months and the knees and ankles had been acutely painful and swollen for a few weeks.

A dull pain in the lower epigastrium, a sense of fullness and distress were more or less constantly present and only slightly exaggerated by foods and fluids and not accompanied by belching, nausea, or vomiting. His past history gave no clue to etiologic factors and his family history was likewise irrelevant.

The *physical examination* revealed a pale, emaciated, asthenic individual with an anxious, pinched expression. The skin was pale and sallow, with a "café au lait" tint to it. The nasal mucosa was covered with dried blood. The mouth showed sordes, tender bleeding lips and gums, several crowned and devitalized teeth, and septic tonsils. The thyroid isthmus was enlarged. The cervical glands were palpable. The carotid throbbing was quite conspicuous. The percussion note over the apices was impaired. The breath sounds were harsh and a few râles were present.

The *heart* was enlarged. The apex impulse was diffuse, extending from the third to the sixth intercostal space and from the midclavicular to the anterior axillary line. Pulsation was also visible along the right sternal border and in the second right interspace. A long systolic thrill was felt in the aortic area and up into the neck. The point of maximum intensity of the apex impulse was 12.5 cm to the left of the midsternal line. The cardiac dullness extended 13 cm to the left and 3 cm to the right of the midline. The retromanubrial dullness was not increased and measured 5.5 cm. The pulmonary second sound was moderately accentuated, while the aortic second sound was faint and impure. The first sound at the apex was loud and sharp, the second was faint. The heart rate was 120 and the rhythm was regular.

A loud, rough aortic systolic murmur was heard transmitted to the neck vessels and a high pitched aortic diastolic murmur was heard trans

mitted to the apex. A high-pitched, well-transmitted apical systolic murmur replaced the mitral first sound and a short, rumbling, late, apical, diastolic was heard. The blood-pressure was 100/75.

The *abdomen* was distended, slightly convex, with the greater prominence on the left. The spleen was greatly enlarged and extended down to the level of the umbilicus. The liver was likewise enlarged, but not to the same degree, and extended 4 cm. below the costal margin. There was some tenderness over the enlarged liver and spleen.

The fingers were cyanotic and clubbed. The radials and brachials were not abnormal. The legs were covered with petechiæ. The reflexes were normal. The T P R. record averages were 102° F, 120, 22.

The blood showed 50 per cent hemoglobin, 3,750,000 erythrocytes, and 2500 leukocytes, with a fairly normal differential count and definite poikilo-

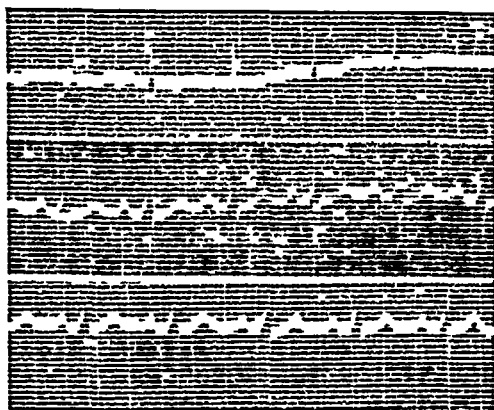


Fig 190—Case XVIII. Definite left ventricular preponderance, T<sub>1</sub> slightly inverted.

cytosis and anisocytosis. The urine contained albumin, many coarse granular casts, leukocytes, and erythrocytes.

The *x-ray* showed a moderately enlarged heart measuring 16 cm. transversely.

The *electrocardiograms* (Fig 190) showed definite left ventricular preponderance.

The patient continued to run a septic fever and lost ground gradually. Epistaxis attacks were frequent and required adrenalin packs. Two crops of petechiæ appeared at about six-week intervals. Ten blood-cultures were negative. About eight weeks after admission he developed a pain in the chest and hemoptysis. His leukocytosis rose to 25,000 and his fever to 104° F. The signs of consolidation were found in the right chest. Blood-cultures showed pneumococci. The patient died.

The autopsy showed aortic and mitral subacute bacterial endocarditis with healing, intracardiac aortic mycotic aneurysm, multiple anemic infarcts

in the spleen and kidneys and hemorrhagic infarcts of the lungs, terminal pneumonia, subacute degenerative parenchymatous nephritis, extreme chronic passive congestion of the spleen with large hemorrhagic anemic infarcts, and extreme nutmeg liver with early central fibrosis. Congestion and edema were quite generalized.

*Discussion*—The patient is unusual in that he presented evidence of practically all of the unusual symptoms and complications that might be encountered in subacute bacterial endocarditis with all its protean manifestations. The case at first appeared to be one of severe anemia or some other blood dyscrasia. Then the picture apparently suggested malaria. The acute pains in the flank and the hematuria suggested renal calculus. The urinary findings indicated severe renal irritation and actual nephritis. The other acute abdominal pain was apparently due to splenic infarction and the chronic abdominal pain was the result of congestion. The central fibrosis of the liver vein increased still more the splenic congestion, much of which was due to cardiac failure. The pallor, epistaxis, bleeding mucous membranes, spongy gums, and ecchymoses suggested purpura or leukemia, but the blood studies ruled these out. The anemia, leukopenia, along with the splenic and hepatic enlargement, suggested Banti's disease. The acute headaches and mental clouding and confusion were undoubtedly the result of cerebral emboli.

In spite of the ten apparently negative blood-cultures the whole picture could scarcely be accounted for by anything other than subacute bacterial endocarditis with multiple emboli with vegetations on the aortic and mitral leaflets.

*Genesis of the Atypical Symptoms in Cases of Heart Disease.*—The theories as to the causes of each of the unusual manifestations of heart disease are numerous, but also interesting. I will mention what seems to be the most generally accepted explanation of the pathologic physiology upon which the manifestation may be based.

The *acute abdominal crises*, whether accompanying coronary sclerosis with angospasm or thrombosis or in cases of sudden changes in the cardiac rhythm, may be considered a manifes-

tation of a rapid engorgement of the liver, the immediate result of the acute cardiac failure. The acute myocardial insufficiency is promptly reflected in the rapid distention of the liver by the stasis of venous blood. The rapid dilatation suddenly stretches the capsule of the liver (Glisson's) and the enveloping peritoneum, which stretching is responsible for the symptoms. The sudden sharp pain is due to the stimulation of the afferent viscerosensory fibers. The glissonian capsule receives some filaments from the phrenic nerve which takes its origin from the third, fourth, and fifth cervical segments. The sympathetic innervation of the liver is through the white ramus from the sixth to the ninth thoracic cord segments inclusive and the left vagus. The increased intrahepatic pressure due to the venous engorgement of acute heart failure and the tension of the stretched capsule will cause viscerosensory and visceromotor reflexes through the sixth to the ninth thoracic segments, which supply the area from the level of the xiphoid to that of the umbilicus. This would account for the usual localization of pain, hyperalgesia, tenderness, and rigidity to the right upper abdominal quadrant. The jaundice, nausea, vomiting, and occasional hematemesis may be accounted for by the liver engorgement, and the portal stasis with the resultant engorgement of the abdominal viscera. The fever and leukocytosis can in some cases, I believe, be explained on the basis of slight but wide-spread cellular changes in the liver parenchyma as a result of the stasis and pressure which result in insufficient oxygenation, acute anoxic changes, fatty degeneration, and atrophy, proteolysis enough to produce a reaction. In cases of cardiac infarction the absorption of protein of the necrotic myocardium is the cause of fever and a high polymorphonuclear leukocytosis, according to Libina, Levine, Wearn, and others.

The *more chronic types of abdominal disturbances*—pain, dyspepsia, etc.—that are associated with heart disease may be explained on a similar but more slowly progressing passive congestion of the liver and portal system of a gradually increasing myocardial insufficiency.

The *psychic disturbances* in cardiac cases are associated with

vascular changes in the brain, anemia or stasis in general, or in the special centers. Other factors, such as a psychopathic constitution, an associated brain disease from multiple small emboli or hemorrhages, as in some cases of subacute bacterial endocarditis, or asphyxia or syphilitic or arteriosclerotic cerebral vascular or parenchymal disease may play a part. Associated acidosis or nitrogen retention or digitalis intoxication have been considered to be accessory factors in the production of psychoses in patients with heart disease.

The *pulmonary symptoms* are primarily dependent upon the venous engorgement of the pulmonary veins and capillaries. In acute failure of the left heart acute pulmonary edema with profuse frothy blood-tinged sputum may be the presenting sign along with severe orthopnea, ashen pallor, and cyanosis.

In the more chronic types of myocardial insufficiency the veins and capillaries of the lungs are chronically engorged. The vital capacity is reduced and the venosity of the blood is increased at the same time the hydrogen-ion concentration of the blood and the tissues of the medulla (Gesell) rise. Any slight overstrain and embarrassment of the heart is sufficient to upset this temporary and limited adjustment and result in a *sharp attack of paroxysmal dyspnea* that superficially resembles an asthmatic attack. *Pulmonary hemorrhage* results from the further engorgement of the vessels that were distended to the limit, the verge of rupture, before the acute overstrain came on.

*Cough* is considered to be due to bronchial irritation, excessive mucus secretion without or with a low-grade infection, the result of the pulmonary congestion. It is sometimes due to irritation of the left recurrent laryngeal nerve from the pressure of a dilated pulmonary artery, with the increased pulmonary blood-pressure, that one finds especially in mitral stenosis, or from an enlarged aorta or subclavian, as in aneurysm. The left recurrent laryngeal nerve loops about the aortic arch between the latter and the pulmonary artery, while the right loops about the subclavian. The paralysis of the vocal cord narrows the air passage to the lungs and increases the asphyxia.

The *nocturnal* attacks of the so-called *cardiac asthma* are brought on often by the loss of a "pillowed-up" position of the orthopneic patient during deep sleep and relaxation. The reasons why the propped-up position makes breathing easier are many. The phenomenon is best explained on the basis of an increased capacity of the lung when the diaphragm descends deepest, as it does in the more erect positions, to a slower inflow into the lungs and, consequently, a better depletion of the pulmonary vessels with each systole, and to a better drainage of the medulla, reducing the venous stasis, diminishing the exposure of the respiratory center to increased carbon dioxide and hydrogen-ion concentration in the blood and tissues of the center itself.

A further explanation of the sudden onset of respiratory distress is that the respiratory center is less sensitive during sleep and allows a slight asphyxia to develop, while the relaxation of the laryngeal muscles narrows the passage and adds to the gradually developing asphyxia, and as a result any slight change, as a decline in position, is enough to precipitate an attack.

The mechanism of the pulmonary disturbances produced by *aneurysms* is simple enough and the effects of the pressure on the bronchi and the trachea with the resulting occlusion are evident in the illustrative cases. Pressure on the recurrent laryngeal nerves with paralysis of the vocal cord often plays a conspicuous part.

The valvular lesions and congenital septal defects produce pulmonary disturbances by increasing the volume of blood in the lungs. *Defective interventricular septum*, with the higher pressure of the left ventricle usually forcing the blood into the right heart, the right ventricular pressure rises, and the rise in pressure is transmitted through the whole pulmonary circuit and an active congestion is the result. *Mitral stenosis*, on the other hand, produces a passive congestion and the back pressure engorging the pulmonary veins and capillaries. Capillary bleeding is common in any congestion of the lungs.

The pulmonary artery dilates sufficiently at times to pinch between itself and the aorta the left recurrent laryngeal nerve. This explains the hoarseness and aphonia with paralysis of the



left vocal cord which is occasionally encountered in mitral stenosis. The acute cardiac pain simulating angina pectoris that sometimes occurs in mitral stenosis may be due to pressure on and temporary occlusion of the left coronary artery by the engorged left auricle (Sternberg). The signs suggesting infiltration and moisture in the left apex in some cases of mitral stenosis may also be attributed to direct and indirect pressure of the dilated left auricle interfering with the drainage of the lung or collapsing it.

The protean manifestations of *endocarditis*, especially the subacute bacterial type, are dependent upon embolism into vital organs, the chronic toxemia and cardiac failure. Embolism and infarction of the spleen produce pain and disturbances in the left upper quadrant. Similar phenomena in the kidneys result in colic and hematuria, suggesting renal calculus. Embolism of the brain may produce paralysis when a motor center is involved, and merely sharp headaches and mental confusion when other cortical areas are infarcted. Pulmonary infarction with the picture of pneumonia appear only when the right heart and tricuspid valves contain thrombotic masses or vegetations. Paradoxical embolism through a congenital defect is quite a rarity.

Subacute degenerative nephritis is the result of a combination of embolism with infarction of the glomerular tufts and the degeneration due to toxemia, and often the passive congestion of heart failure. The café au lait color, slight pigmentation and pallor, the anemia, purpura, and the epistaxis are the result of the toxemia.

**The Differential Diagnosis of the Unusual Manifestations of Heart Disease**—The apparent urgency of the situation, which usually results in the admission of the patient with abdominal crises to a surgical service, is responsible for many of the serious errors in the diagnosis of cases of heart disease presenting atypical symptoms. A careful history and especially a careful physical examination usually reveal some reliable signs of heart disease, as was demonstrated in most of the cases cited. There is, furthermore, usually evidence of grave lesions and myocardial insufficiency. The *electrocardiographic studies*

yielded the most conspicuous evidence of serious heart disease in practically all cases. The ease with which these studies can be made, the reliability and value of the findings commend the method in all borderline cases. I do not wish to be understood as indicating that all cases of heart disease show abnormal electrocardiograms or that all cases in which the symptoms are not due to heart disease show normal electrocardiograms. I wish only to impress upon you the fact that an abnormal electrocardiogram in a borderline case makes the likelihood of the exciting cause being cardiac quite probable. This should lead to a most careful survey of the whole case with this point in view.

The differentiation of some of the abdominal crises in cardiac cases from primary abdominal lesions is at times almost impossible. This is especially true when there is rigidity, fever and leukocytosis, and sometimes jaundice, all of which I am prone to attribute to the acutely congested liver. The visceromotor reflexes are not extensive and not so sharply bounded as are the viscerosensory reflexes, therefore the *rigidity* from the acutely congested liver is less marked and more circumscribed than is the hyperalgesia which extends from the sixth to the ninth segments inclusive. In other acute abdominal lesions the areas of hyperalgesia are much the same. The *fever* in liver congestion is, as a rule, not as high, does not continue to rise, and usually does not persist as it does in primary abdominal conditions. The *leukocytosis* may rise as high as in an infectious case, but the proportion of neutrophilic polymorphonuclears does not rise above the normal proportions in the few cases that I have seen. In myocardial infarction and necrosis Libman has demonstrated a high polymorphonuclear leukocytosis. This differential diagnostic point needs further study.

The *pulse* and *blood-pressure* changes the degree of *shock* and *collapse*, and the increase in *respirations* are usually greater and there is distinct cyanosis and dyspnea in the acute cardiac failure case. The patient with pneumonia and abdominal symptoms also presents cyanosis and tachypnea, but the temperature and polymorphonuclear leukocytosis are higher, while there are no hyperal-

gesic areas and the abdominal tenderness is more superficial, is often relieved by pressure, and is accompanied by only voluntary rigidity. Voluntary rigidity usually shows momentary relaxation at the end of expiration and the beginning of inspiration, under gentle palpation with a warm hand and when the patient's attention is distracted. Involuntary rigidity indicates peritoneal irritation and never relaxes as long as there is irritation. Even morphin will not relieve the spasm, complete general anesthesia alone will remove it.

The *tenderness* in the cardiac case with abdominal symptoms is due to the tenderness of the engorged liver, which is always palpable in the right upper quadrant. In primary abdominal conditions tenderness is due to localized parietal peritoneal inflammatory processes and is localized to the area involved. Hyperalgesia is differentiated by the fact that the pain persists in the skin and subcutaneous tissues when they are grasped and drawn away from the deeper structures. The hyperalgesia is elicited by slight touching of the skin. The hyperalgesic areas are not directly over the affected organ and are not shifted with a shift in the position of the diseased organ.

The early genuine *abdominal pain* is referred pain, later the pain is localized to the diseased organ as the disease process involves the adjacent parietal peritoneum.

The *liver* and *gall-bladder* area extends from the third to the ninth dorsal segment, inclusive, with its maximum point in the lower epigastrium to the right at the intersection of the parasternal line with the horizontal line through the tip of the tenth rib. The traditional reflex through the phrenic in the diaphragm to the right shoulder and the angle of the scapula is sometimes present. The area of *duodenal* and *gastric* disturbances is from the fourth to the eighth segments, from the ensiform to the umbilicus, with the maximum midway down and slightly to the right of the midline for duodenal and slightly to the left for gastric lesions.

The *small intestine* and appendix area is from the eighth to the eleventh segments, which is about the umbilicus with the maximum point one-fourth the way down the midline from the

umbilicus and one-third the way from the umbilicus to the right anterior superior spine

The area of the *large intestine* is below the eleventh segment in the midhypogastric region with its maximum point in the midline three-fourths of the distance down from the umbilicus to the symphysis

The *fallopian tube* areas are similarly located in the iliac or inguinal regions with the maximum point one-fourth the distance up from the middle of Poupart's ligament to the umbilicus

In the abdominal crises from an acutely congested liver of sudden heart failure the *liver dulness* is definitely increased. An *obliteration* or *disappearance* of the *liver dulness* is evidence of free gas in the peritoneal cavity between the liver and the diaphragm. This is almost pathognomonic of the *perforation* of an abdominal viscus which presents a sudden onset of excruciating pain, severe initial shock, and board-like rigidity

*Abdominal distention* or meteorism may be present in the cardiac as it is in primary abdominal lesions. It is serious when definitely progressing. In intestinal obstruction, especially when due to intussusception, volvulus, or tumor, there is ballooning of the bowel, cessation of the passage of flatus, progressive distention along with a persistence of vomiting, and in the later stages fecal vomitus

Tabetic crises may occasionally be complicated by volvulus and present the picture of obstruction. Without complications, however, the tabetic crises show no distention and the vomiting in severe cases may persist for two to three days. The vomitus is copious mucus and bile and occasionally blood tinged, but never fecal. The bowels continue to act freely. The pains are lancinating and may be felt in the flanks, girdling around the abdomen between the shoulders and in the extremities. The other signs of *tabes dorsalis* are, however, usually in evidence

It is evident from this discussion that no one finding or sign is sufficiently pathognomonic to base a diagnosis on. A careful combination study of many findings, symptoms, and signs is necessary in the solution of problems in the differential diagnosis of acute abdominal crises

The more *chronic types of abdominal disturbances* due to cardiovascular lesions are perhaps even more frequently erroneously diagnosed than are the acute types. The portal stasis with congestion, especially of the stomach wall, results in secretory disturbances such as one might get in gastro-intestinal diseases. The mucous secretion is increased, while the acid secretion is usually reduced, often to the point of producing an achlorhydria. Slight trauma may be sufficient to injure one of the engorged vessels and hemorrhage results. The chronic passive congestion of the liver, the edema, the reduced exercise tolerance, the evidences of myocardial insufficiency, along with the physical and electrocardiographic findings of heart disease, should be carefully looked for in all borderline cases. The gastro-intestinal x-ray studies are usually negative except for an enlarged liver. The competent roentgenologist, who has a good fundamental knowledge of internal medicine, not infrequently notes the enlarged liver, enlarged heart and aorta, and directs attention to the cardiovascular system. The study of the latter system then yields the necessary evidence for the solution of the problem.

The *psychic disturbances* rarely mask the primary heart condition. The mental confusion, hallucinations, and delusions are usually mild, come on at nightfall, and clear up at day-break. Irritability and melancholia, acute mania, and depression may be the presenting symptoms, but the evidences of heart disease are conspicuous enough in most instances.

The so-called *cardiac asthma* is typically a paroxysmal attack of simple rapid breathing, tachypnea, with no impediment to inspiration or expiration, while bronchial asthma is produced by a spasm of the bronchial musculature and a fixation of the diaphragm. The bronchial stenosis hinders inspiration, but the strong inspiratory muscles overcome this, while the weaker expiratory muscles are less effective, expiration is prolonged with accompanying wheezing squeaks, râles, and emphysema. The cardiac case usually shows some râles from pulmonary edema and is not infrequently complicated by a chronic bronchitis. Chronic bronchitis cases often suffer from asthmatic

attacks which are initiated and accompanied by severe paroxysms of coughing

Antispasmodics, atropin, and epinephrin relieve bronchial asthma and asthmatic bronchitis attacks, while strophanthin and digitalis relieve the "cardiac asthma" attacks. The cardiac patients who suffer paroxysmal attacks of dyspnea usually show much evidence of myocardial insufficiency. The aortic dyspnea that may precede or accompany anginal attacks, and is associated with the sense of constriction, oppression, and imminent dissolution is less well understood and presents fewer evidences of heart disease.

The pulmonary symptoms and signs resulting from the pressure effects of *aneurysm* are usually accompanied by the classical signs of aneurysm and the fluoroscopic x-ray findings are confirmatory. Occasionally, when laminated clots obscure the pulsations the differentiation from solid tumor is extremely difficult. The diagnosis of a dissecting aneurysm must rest much on inference.

The differentiation of *mitral stenosis* and *congenital defect* of the intraventricular septum depends on the recognition of the characteristic physical signs of these lesions. The signs are usually well developed. The electrocardiographic findings are usually characteristic and the x-ray studies reveal pathognomonic changes in the cardiac outline and suggestive changes in the pulmonary vascular system. The absence of the symptoms of toxemia and of acid-fast organisms in the sputum constitute valuable evidence against the diagnosis of pulmonary tuberculosis.

The *rhythm disturbances* are as a rule, easily recognized at the bedside. Any irregularity that persists with a heart rate of 120 usually is, and of 140 or more always is, auricular fibrillation. Likewise any rhythm, regular or irregular, at or below 40 per minute is quite probably heart-block. The electrocardiograms are absolutely diagnostic of these disturbances. The important point to recognize is that these rhythm disturbances especially when acute, may be associated with acutely congested liver, producing sudden severe abdominal pain, fever, and leukocytosis of the same character described above.

*Pericarditis* practically always presents a pericardial friction rub at some time in its course. Warthin's sign of an abnormally sharply accentuated pulmonary second sound, and Christian's sign of compression of the left lung, opposite the angle of the left scapula, are suggestive findings and should lead to further cardiac studies. The electrocardiograms in cases of pericardial effusion often show minute low voltage complexes. In rare instances the clinical pictures of acute appendicitis and perforated gastric ulcer have been associated with a pericarditis. I have not been fortunate enough to recognize any such case up to the present time.

*Endocarditis* with all its protean manifestations is, as a rule, recognized because of the combination of such a multiplicity of signs of embolic system involvement. The heart practically always presents an aortic or a mitral diastolic murmur. The spleen is almost invariably enlarged. The urinary sediment routinely shows erythrocytes. Fever, petechiæ, tender cutaneous nodes (Osler), tender sternum (Libman), pigmentation, emaciation, and positive blood-cultures are present at some time or another. In a previous clinic (Medical Clinics of North America, 1923, vi, 1237) I described 4 cases that simulated subacute bacterial endocarditis very closely, but were proved to be other conditions. One case with persistently negative blood-cultures was described as a case of endocarditis, as autopsy later proved it to be. The relative differential diagnostic values of the various findings are assigned or apportioned in this previous article.

**Treatment of the Unusual Manifestations of Heart Disease —** Treatment can only be touched upon very briefly. In coronary spasm or thrombosis immediate complete and continued rest in bed under morphin is indicated. Vasodilators are in order as soon as coronary spasm or thrombosis is suspected. Amyl nitrite, 3 to 5 minims, usually in pearls, should be administered by inhalations, nitroglycerin spirits, 1 to 2 minims, or one tablet, 0.0005 gm (1/100 gr), given under the tongue, and erythrol tetranitrate tablet 0.05 gm (1 gr), every two or three hours.

Euphyllin (theophyllin ethylenediamin) is a most promising drug because it distinctly increases the coronary flow (Fred

M Smith) It is given in 0.48-gm ( $7\frac{1}{2}$  gr) doses two to four times a day. In urgent cases it is given well diluted intravenously, from specially prepared ampules, or intramuscularly in a more concentrated solution, or per os in tabloid form, or per rectum in suppositories.

Benzyl succinate, 0.4 gm (5 gr), two or three times a day, will often relieve and ward off minor coronary angiospasm and can be used over long periods of time.

Iodids and mercury have been long in use in cases where syphilis is the etiologic factor, and often also where involutary arteriosclerosis is the only recognizable basis of the symptoms. Potassium salts do reduce conduction, and where conduction defects are shown by the electrocardiogram I believe it is safer to use some other salt, as sodium iodid. Since arsphenamin is also poorly tolerated in cardiovascular lues, the use of bismuth salicylate, 0.30 gm (2 gr), injected intramuscularly every five days, as suggested by Professor J. H. Musser, seems to be the most rational treatment. I have recently had the opportunity of following a patient with syphilitic aortic regurgitation who developed heart-block with a series of very severe Adams-Stokes attacks after less than a week of mixed treatment with potassium iodid by mouth and mercury by inunction. Bismuth salicylates is, however, well tolerated.

In heart-block with Adams-Stokes attacks and with acute liver engorgement barium chlorid in 0.030- to 0.050-gm ( $\frac{1}{2}$ - $\frac{3}{4}$  gr) doses every three hours, as suggested by Drs. A. E. Cohn and S. A. Levine, has proved most satisfactory in bringing my patient out of a stormy series of attacks and putting him back on his feet.

When increased vagus tone is responsible for the block, atropin sulphate 0.0006 gm ( $1/100$  gr), every three hours or less frequently will keep the vagus pretty well paralyzed. Sometimes, however, the increase in auricular rate following atropin increases the degree of block. Electrocardiograms enable one to treat these patients most intelligently.

In paroxysmal auricular fibrillation, where the acute rhythm disturbance is threatening the life of a patient and where acute



abdominal symptoms are presenting, it is not unduly heroic therapeutics to use quindin sulphate. The drug can be given well diluted in doses of 0.130 to 0.190 gm (2-3 gr) intravenously without much, if any, more danger and with much more definite results than when given by mouth in doses of twice the size by mouth at six-hour intervals. The test for idiosyncrasy with a small dose, 0.065 to 0.130 gm (1-2 gr), by mouth should be carried out, or one-tenth this amount by vein should be tried whenever the case is not too urgent.

In the more chronic types of heart failure prompt and complete digitalization is indicated whether auricular fibrillation or normal mechanism is present. In cases with delayed conduction atropinization will, as a rule, allow digitalization without blocking. Venesection, with the withdrawal of 500 c c of blood, will often relieve a greatly embarrassed heart and a congested vascular system and initiate a period of progressive improvement. Valvular lesion and congenital lesions, as mitral stenosis and defective interventricular septum with great pulmonary congestion, are greatly relieved by bleeding. Not infrequently spontaneous hemorrhages serve to tide the patient along.

Aneurysms usually do not respond very favorably to anti-luetic treatment, especially when they have reached the point of producing pressure symptoms. At times the rapidity of the progress of the lesion may be checked. Surgical wiring and electrocoagulation occasionally yield favorable results. Intra-thoracic arterial and cardiac surgery is, however, still in its infancy. We can expect great developments in this field within the next decade.

Infections, pericarditis, and endocarditis do not respond uniformly to treatment. Salicylates in large doses, 2 grains per pound of body weight (0.2 gm per kilo) per day, is about as effective as any remedy that we have. In some cases organic dye-stuffs injected intravenously have proved effective. Capps has reported favorable results from the use of sodium cacodylate injections. No specific medication has been discovered as yet. The complications of the infections must be treated more or less symptomatically. The severe anemia and uremia do not respond

to the ordinary therapeutic procedures and the prognosis is, as a rule, hopeless

**Summary**—An outline of the unusual manifestations of heart disease is presented

Illustrative case histories with electrocardiograms are given in detail

The genesis of the atypical symptomatology is discussed

The differential diagnostic points are briefly outlined and the importance of the electrocardiographic findings is emphasized

The treatment of the various conditions is mentioned, with specific directions given for the emergency cases only

Each of the groups of the unusual manifestations is more fully discussed in individual articles in the literature I will, therefore, append a bibliography of selected studies which are well worth your careful attention

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# CLINIC OF DR SIDNEY K SIMON

## TOURO INFIRMARY

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### SOME UNUSUAL CLINICAL TYPES OF ENTAMEBIC DYS- ENTERY

You are more or less familiar with the characteristic clinical picture of a case of chronic entamebic infection of the large bowel. When the patient first presents himself for observation there is a history, as a rule, of a marked disturbance of bowel functioning with abdominal pain, these symptoms having extended intermittently over months, and in some instances over a period of several years. The outstanding feature in the average case is the persistent tendency to loose bowel passages upon the slightest provocation, which is usually dietetic in origin, though provoked at times even by simple changes in atmospheric conditions. The diarrheal movements are also often attended by varying degrees of rectal tenesmus. As distinguished, in the main, from other types of diarrhea, the stool passages in entamebic colitis quite constantly contain blood, either as a frank hemorrhage of pure reddish blood or else as blood-streaked or stained mucus.

Even without resort to any formal treatment in many instances it will be found that the various bowel symptoms exhibit a tendency to subside gradually, and the diarrheal condition, in fact, is subsequently succeeded at times by periods of rather obstinate constipation. Relapses are common, however, without obvious cause in some cases, so that the entire course of the disease runs a very irregular and uncertain course.

Again, from the earliest stage of the onset of the infection the patient exhibits certain departures from the normal health standard quite apart from the intestinal outbreaks. The evidence thus suggested of a constitutional toxemia in the disease

includes, besides a variety of digestive complaints, such as epigastric bloatedness and heaviness, and impairment of appetite, also a progressive loss in weight, the blood-picture of a low-grade secondary anemia, and, in general, a lack of physical vigor to which the patient had been previously accustomed. This constitutes in brief a résumé of the ordinary course and symptomatology of the average case of chronic infection of the large bowel with pathogenic entameba.

My purpose at the present time, however, is not to dwell at length upon the already well-known clinical phases of the disease, but to focus attention rather upon some of the more unusual types of cases which have passed in review in our hospital and ambulatory service. Chiefly characteristic of this selected group of cases is the fact that knowledge of the existence of a pathogenic protozoal infection of the bowel could scarcely have been obtained from the clinical history or physical findings. On the contrary, these were in some instances rather of a contradictory nature. The ultimate diagnosis rested solely upon the discovery of *Entamæba histolytica* in the stools, either in the vegetative or encysted forms. The finding of the typical organisms in the bowel passages or from scrapings from the rectal wall remains, after all, the sole criterion of the existence of the infection. In the following case histories which will be submitted the need is emphasized for regular routine stool examinations in every potential intestinally ill individual, regardless of whether the symptoms point directly to protozoal infestation or not. In a broader sense the necessity of this procedure is likewise indicated in every diagnostic study, and particularly in those parts of the country where entamebic disease is known to prevail endemically.

**Case I**—White female, aged thirty-two years, unmarried, native of Mississippi, has complained for the past four years of an aching sensation in the epigastrium, which radiated toward the left upper abdomen and back. The pain was most acute upon awakening in the morning. The patient also awoke during the night with abdominal distress, which was relieved by the movement of gas in the bowel and by the taking of alkalis. During the day there was a feeling of fulness and distention in the abdomen after eating, associated at times with nausea and occasional vomiting. A history of mild

constipation dated back to early childhood. The appetite was good and there had been no loss in weight. The physical examination revealed no noteworthy features. Adipositas was well marked and sensitiveness upon deep pressure was present over the entire abdomen, particularly in the left upper abdomen. The gastric analysis revealed moderate hyperacidity. The Wassermann reaction was negative. Otherwise, the blood-picture was that of a moderate secondary anemia. Urine negative except for an excess of indican. Much to our surprise, an examination of the stool displayed the presence of actively motile vegetative *Entamoeba histolytica*. Following purgation the mucous membrane of the lower bowel was inspected by proctoscope, but no evidence of ulceration was detected. The radiologic examination of the colon likewise showed normal haustra without filling defects.

*Comment*—In this case it is to be noted that there was no history of diarrhea or dysentery at any time in the past, but, on the contrary the patient had been subject to constipation, for which purgatives were frequently employed. The finding of the pathogenic entameba in the feces was indisputable evidence of the presence of a nest of infection in the wall of the large bowel. From the history in this case the location of the main lesions was most probably in the neighborhood of the splenic flexure since the pain and tenderness were centered in this region.

**Case II.**—White male, age twenty-four, single and resident of Mississippi. The clinical notes taken in this case include essentially the following details. For the past nine months the patient has been running a mild degree of temperature averaging between 100° to 100.5° F. each afternoon without the occurrence of chills or sweats. He also complained of excessive abdominal gas with sour belching, coming on a short while after eating. In the mornings he awoke with a bad taste and a coated tongue. The bowels have been very costive for the past year, requiring large doses of purgatives for relief. Numerous doses of calomel medication had been administered. There was a feeling of languor even after slight exertion. The patient was about 15 pounds below his average weight. Pallor of the skin was also quite marked. The appetite was poor. Tonsillectomy had been done nine months previous to consulting me, and three weeks after removal of the tonsils a nest of hard, enlarged glands were removed from the postcervical region. The pathologic examination of these glands showed chiefly chronic inflammatory tissue without definite etiology. They did not appear to be connected with the diseased tonsils, according to the pathologist's report.

Physical examination showed heart and lungs to be normal. The blood-pressure was 110 systolic and 60 diastolic. The abdomen was found to be distended with gas, with a barely palpable liver edge. The spleen was not palpable. No sensitive areas in the abdomen were discovered. The radiologist's report made note of some adhesions around the terminal ileum with

dilated coils, suggesting a Lane kink. The large bowel was negative except for hyperspasm and stasis. Examination of the urine and gastric contents proved approximately normal. A number of Wassermann tests were made and proved negative. The hemoglobin blood content was found to be around 75 per cent, with a moderate decline in red cells. Malaria plasmodia were absent. In the course of a routine examination of the feces numerous *Entamæba histolytica* were found, both the vegetative and the encysted types.

*Comment*—At the time that I saw him the patient had been treated for a number of tentative ailments, but no clear-cut diagnosis had been made. At one period he was kept in bed for three weeks on an exclusive milk diet. Several courses of quinin medication had also been employed. Neither the afternoon rise of temperature nor the languid feeling had, however, been relieved. While increase of temperature is not a common feature in the chronic or latent types of *Entamæba histolytica* infection, cases are occasionally encountered with this phenomenon. It is interesting to speculate upon the connection of the entamebic infection in this case with the chronically inflamed cervical glands, which had been removed at a previous operation. Kofoed and his followers in California have called attention recently to the more extensive distribution of *Entamæba histolytica* in the various tissues of the body outside of the large bowel. Secondary invasion by means of the portal and general circulation to the liver, spleen, and brain are well-known instances of the migrating possibilities of the organisms. Kofoed, among others, claims to have found evidence of the presence of typical pathogenic entameba in the bone-marrow and articular structures in cases of chronic arthritis. Armstrong likewise calls attention to the occurrence of retinitis and other ocular lesions as a result of entamebic infection. Warthin has also demonstrated *Entamæba histolytica* in the testes. In the present case the organisms, unfortunately, were not sought for in the inflamed cervical glands, due to the fact that no suspicion of entamebic infection had been entertained at the time. Apart from this phase of the case removal of the entamebæ from the bowel resulted in a complete recession of the afternoon temperature. Incidentally, the patient gained 11 pounds within

three months after treatment, and the blood-picture also returned to the normal standard within the same period of time

**Case III**—White male, age forty-four, single, a tinsmith by occupation. For the past five years this patient had been conscious of a bearing-down sensation in his pelvic region associated with an aching pain over the sacrum and in the hips and thighs. He claimed to have noticed at times a swelling in the neighborhood of both hip-joints. He had been treated variously for rheumatism and sacro-iliac subluxation. His bowels showed a constant tendency to constipation, but it was noted that laxatives usually relieved the discomfort in the back and thighs. Abdominal gas was increased shortly after eating. Frontal headaches have been frequent, especially in recent years. His digestion has always been good and there has been no impairment of appetite. The patient has also marked a gain in weight during the past year. Since an attack of influenza one year ago the bowels have shown a tendency to looseness, but the patient claimed never to have seen any blood or mucus in the passages. The test breakfast showed an entire absence of hydrochloric acid with a very low total acidity, the gastric motility was normal. Moderate decrease in red blood-cells was present, namely, 3,473,000, with 50 per cent hemoglobin. The Wassermann reaction was negative. The urine examination was without noteworthy features. Physically, no special abnormalities were found with the exception of the skin pallor, and an extensive pyorrheal condition of the gums. No suspicion of entamebic infection of the bowel was entertained until the actual discovery of the organisms in the stool was made. Proctoscopically, no ulceration could be found, though the rectal mucosa appeared inflamed and slightly granular. The radiologic examination after a barium meal was entirely negative with the exception of a highly spastic pylorus.

*Comment*—This patient was inclined to trace the rather mild degree of bowel looseness to an attack of influenza one year previous, and had not considered the condition of sufficient importance to necessitate treatment. His chief complaint centered about the persistent bearing-down sensation and nagging, aching pain in the back and thighs, and he came to us with the idea that possibly hemorrhoids were responsible for this. Following treatment for the entamebic infection he gained 17 pounds in weight within four months. His blood-picture became approximately normal, and he was relieved entirely of the bearing-down back and hip discomfort. The occurrence of an achylia gastrica in this case in connection with the entamebic infection should not be considered of any especial significance. A careful record we have kept of the gastric acidity figures in



entamebic cases has convinced us that the infection itself apparently possesses no direct bearing upon the secretory apparatus of the stomach

**Case IV** —White male, aged fifty-five, a native of Mississippi, and a saw mill superintendent by occupation. The chief complaint for which this patient consulted us was a constant sensation of aching pain and soreness localized in the left lower abdomen, apparently made worse by physical effort. This symptom had been present for about eight months. The bowel movements were described by the patient as normal in size and consistency, and he had but one evacuation per day. A few months prior to the onset of the pain he had made note of occasional spells of loose bowels accompanied by a slight degree of tenesmus. A small amount of mucus was present in the stools, mostly as a covering of scybulous masses, but there was no blood. Since the onset of these mild intestinal disturbances he had also noticed a bloated, heavy feeling in the upper abdomen, appearing shortly after eating, with occasional acid stomach and sour belching. During the past six months he had lost 20 pounds in weight, namely, from 178 to 158 pounds. Ten years ago he had suffered a fall from a horse and was unconscious for thirty-six hours. A diagnosis of fracture of the ninth and tenth left ribs was made at the time. The patient attributed the pain in the left lower abdomen to this incident, claiming that both the left thorax and left abdomen had not felt entirely free of discomfort since that time. On examination no abnormalities were detected, either in the ribs or in the chest organs. The blood pressure was 110/65. The colon on palpation was found to be contracted and tender to touch, particularly over the sigmoid area. The proctoscope revealed a markedly relaxed anus with only slight injection of the rectal mucosal vessels. No ulcers were found. The test breakfast showed normal gastric motility, with high acidity. The blood and urine examinations were without note worthy features. The discovery of *Entamoeba histolytica* infection in this case was not made until three months after the patient first came under observation, although repeated examinations of the stools had been made. Prior to that all efforts to relieve the apparent sigmoid and descending colon sensitiveness had resulted in failure. Following the ultimate cure of the protozoal infection the abdominal pain and tenderness disappeared entirely. Subsequently, with improved appetite, the patient gained 10 pounds within three months.

*Comment* —The reason for the failure to detect the organisms in the stools in this case after repeated examinations is difficult to explain. However, this is not an altogether uncommon experience, as reported by others. We have found it a good routine practice, therefore, to continue our search for intestinal protozoa whenever intestinal irritation of any kind exists for which no adequate cause can be assigned. Wenyon believes

that at least six examinations of the stools should be made before *Entamæba histolytica* infection can be ruled out in any case

**Case V**—White female, single, aged forty-eight years, native of England, and a resident of this country for ten years, a child governess by occupation. The outstanding clinical symptoms from which this patient suffered were intermittent attacks of nausea and vomiting appearing apparently without definite cause. This condition had persisted for about twelve years, and had previously resisted all plans of treatment. The attacks of vomiting came on usually after the midday meal, and were preceded by a sensation of fulness and heaviness in the epigastric region. She had suffered from an obstinate form of constipation for over fifteen years, and, in fact, had been in the habit of taking a purgative each night. There was no history of outbreaks of diarrhea or dysentery at any time. The patient herself believed that the attacks of nausea and vomiting were connected in some manner with her constipated state. Her appetite remained good and there was no restriction of food.

Upon examination the patient presented the picture of a moderate degree of emaciation, having lost approximately 20 pounds in ten years. She was of frail body habitus with poor muscular development. No enlargement or other cardiac pathology was present, though an occasional arrhythmic extrasystole was noted. The arteries were moderately thickened, with blood-pressure of 175/78. The abdomen was of the Stiller type, with general visceroptosis, no sensitive areas were found along the course of the large bowel or elsewhere. The test breakfast showed rapid gastric emptying with lowered acidity. The blood-picture was that of a very moderate secondary anemia. The urine contained an excess of indican, but no albumin, casts, or sugar were present. In the hardened, constipated feces specimen she had brought for routine examination the cysts of *Entamæba histolytica* were promptly detected, and after subsequent active purgation with salines the vegetative forms also made their appearance. The patient was accordingly placed under amebic treatment, and though an unusual degree of vomiting resulted from the use of ipecac in this case, the removal of the infection was followed by a total cessation of the vomiting spells from which the patient had previously suffered. She gained 11 pounds in weight within three months, and has remained entirely well for a period of three years since the institution of treatment.

*Comment*—This case demonstrates anew the great value of routine stool examination. In no other way could a diagnosis of *Entamæba histolytica* infestation have been possible, since the clinical symptoms certainly did not point to this condition as the causative agent. Vomiting and chronic constipation were the sole factors presented clinically, and both conditions failed of relief until the entamebic infection was discovered and treated.

**Case VI**—White female, aged thirty-two years, single, native and resident of New Orleans, and a stenographer by occupation. This patient consulted us primarily for an unnaturally excessive appetite with which she had been afflicted as she claimed for the past several years. The bulimia in this case was described as a frantic hunger sensation in the epigastrium whenever the stomach became empty, which usually occurred about one hour even after a heavy meal. When a further supply of food was not immediately forthcoming she experienced a feeling of hollowness in the chest with weakness and vertigo. The condition had improved somewhat within the past year under the care of a neurologist. For two months prior to seeing us she had suffered occasional attacks of diarrhea, mostly in the form of soft, semisolid stools, three to six in number, and worse usually during the early morning hours. Neither griping nor tenesmus were present, however, and no bleeding had been noticed in the bowel passages. Previous to this the movements had been well formed, with but one evacuation a day. The patient had been examined at a Group Clinic, had been found free of organic digestive lesions, and had been pronounced a psychoneurotic. There had been considerable loss in weight during the past two years. In spite of the enormous amounts of food ingested, the patient presented a somewhat drawn, emaciated appearance with a moderate skin pallor. The heart and lungs were negative. The blood-pressure was somewhat increased (140/90). No abdominal tenderness was present, and the various abdominal organs were not palpable. On proctoscopy the rectal mucosa appeared pale and friable. No ulcers were found. All the superficial reflexes were highly exaggerated. The blood-picture in this case showed slight deviation from the normal with a total red count of 4,350,000 and a hemoglobin percentage of 75. The gastric acidity was also lowered (hydrochloric acid, 8, total acidity, 32). Gastric motility was unimpaired. The urine was negative. No organic lesions of the nervous system could be made out. The patient had never been seriously ill at any time. In the diarrheal stool we were able to find without difficulty the presence of *Entamoeba histolytica*. The forms were rather small, but the clear differentiation between entosarc and ectosarc left no doubt as to the pathogenic nature of the organism. Following this discovery the patient was relieved of the infection with ipecac medication, and subsequently reported that her former increase of appetite was now within normal range. She also gained considerably in weight after treatment and felt markedly improved in other respects.

**Comment**—A further interesting clinical observation in connection with entamebic colitis is the occurrence of increase of appetite in many cases. In this instance the increase amounted to a condition of true bulimia. Undoubtedly the highly unstable nervous system played an important rôle in this case, as it does in other types of bulimia. However, the prompt relief of the ravenous appetite in this case following treatment for the entamebic infection sets forth a new factor, as far as I know, that

should not be overlooked in the future in searching for the cause of an otherwise unclassified bulimia.

**Case VII.**—White male, aged thirty-six years, iron worker by occupation, and a resident of New Orleans. The past history of this patient showed freedom from illness of all kinds, with the exception of an attack of malaria fever about five years previous, accompanied at the same time by muscular rheumatism. He first came to the clinic eighteen months ago. At this time he was complaining of attacks of hunger pain in the epigastrium appearing most severely about 4 P. M. and followed for several hours by severe cramp pains over the entire abdomen. The pain was severe enough at intervals to require opiates for relief. Following an attack of this kind, the abdomen remained sore and tender to touch for approximately forty-eight hours. There was no history of diarrhea or dysentery. The bowels, in fact, moved regularly each day and were of normal consistency. No loss in weight had been recorded. The gastric analysis failed to reveal evidence of any secretory or motor abnormalities. The blood-picture and urine tests both exhibited negative findings. Wassermann reaction likewise proved negative. Physically, the patient presented the picture of an individual of normal stature, average weight, and good color. The superficial arteries were somewhat thickened, with a relatively low blood-pressure. The chest organs were found normal. The abdomen evinced no evidence of sensitiveness except of mild degree over the sigmoid area. Radiographically a slight prolapse of the stomach was observed, with a moderate dilatation of the second portion of the duodenum. Considerable colonic stasis was found to be present and the rectum was moderately dilated. No flattening of the haustra was noted. Through proctoscopic examination the rectal mucosa appeared smooth and glistening, and no ulcerations were detected. Smears made from particles of the hardened feces revealed the presence of *Entamoeba histolytica* cysts. The vegetative forms were subsequently detected in the liquid stool after saline purgation.

*Comment.*—As in the preceding case, the chief symptoms presented by this patient was an intense hunger sensation in the epigastrium, though this sensation appeared intermittently in this instance, and the interval after eating was from two to three hours. Attacks of severe cramp pains over the entire abdomen was likewise a predominant feature. Originally a tentative diagnosis of peptic ulcer was made, as suggested by the symptoms, but this belief proved untenable in the light of the gastric and radiologic findings. Further proof of the non-existence of peptic ulcer was furnished by the complete relief brought about by the removal of the entamebic infection. Incidentally

this patient has remained entirely well over a period of two years following treatment

**Case VIII**—White male, aged forty-three, married, clerk by occupation, and a resident of New Orleans. This patient is presented in this group because he represents a clinical type not at all unusual in our experience, in that an operation had been performed for a supposed rectal lesion without taking into account the possibility of entamebic infection of the bowel as a cause for the clinical disturbance. He had been a sufferer for two years previous with a painful bearing-down sensation in the anal region, accompanied by tenesmus and frequent stools. In the passages he frequently noticed mucus and blood, in fact, he claimed to have passed small amounts of red blood with each stool. The patient believed that he was a victim of hemorrhoids, and consulted his physician, who, after futile attempts to relieve him, referred him to a rectal surgeon. According to the patient's account no microscopic examination had been made of the feces at any time. An operation was performed in August, 1923 for a growth in the rectum, possibly a polypus. This was removed, but within a short period the rectal distress and bleeding returned. He took various medicines by mouth and also a course of rectal irrigations, which, again, did not bring relief. When I saw him three months ago he was having from four to six soft mucoid stools a day, each containing streaks of blood. The rectal tenesmus was quite marked, and, in addition, he complained of considerable abdominal gas. Since the onset of his trouble he had lost in all about 30 pounds in weight. The digestion was good and no attempt at dieting had been made. On proctoscopic examination the anus was found markedly spastic. The rectal mucosa was studded with numerous superficial ulcerations and the mucosa in general appeared highly injected and extremely friable. Microscopic smears from the ulcerated areas revealed extensive entamebic histolytica infection with the vegetative forms. Upon finger palpation fibrous infiltration of the rectal wall was discovered with a slight narrowing of the lumen. In addition to the rectal pathology, an anterior epispadias of congenital origin was found. The patient apparently experienced no inconvenience from this latter condition. Physically, no other abnormalities were detected, except an increase in arterial tension (160/90). The gastric analysis, blood picture and other tests resulted in practically negative findings.

The patient was given ipecac treatment for the entamebic infection, with satisfactory results. Subsequent proctoscopic examinations showed complete healing of the ulcerated areas and a return to normal bowel functioning. Bougies were used as an after-treatment for the beginning stricture formation.

*Comment*—Failure to examine the fecal contents microscopically in this case unquestionably resulted in an incomplete diagnosis. The nature of the rectal growth for which the patient was operated upon was not forthcoming, but certainly could not have been the sole cause of the rectal disturbance. Our

own records show many similar instances of rectal surgery having been carried out in the face of an undiagnosed entamebic infection of the large bowel. This emphasizes again the need of a routine stool analysis even in the face of other diagnosed lesions.

**Case IX**—White male, aged fifty-four, single, insurance agent, native and resident of New Orleans. Prior to consulting us this patient had complained for five months of a sensation of stiffness of the muscles of the lower extremities upon movement. The stiffness was most noticeable upon arising in the morning. He also complained of a drowsy feeling during the day, and felt as though he could not get enough sleep. A bad taste was also present upon awakening in the morning, but otherwise he had no digestive disturbances. The appetite had always been good and there was no food restriction. The bowel movement had remained regular, with one passage each day. No loss in weight had been noted. The patient gave a history of a typhoid fever attack of mild degree twenty years ago. In 1903 he had malarial fever which responded promptly to treatment. He had been a victim of the flu epidemic in 1919, but without serious consequences. His chief outdoor diversion consists in polo playing, though he was not inclined to trace the muscular stiffness to this source. He had gonorrhea as a young man, but denied syphilitic infection. His habits otherwise had always been good. The laboratory examination resulted in the following findings. The test breakfast showed normal motility with a slight excess of gastric acidity (hydrochloric acid, 45, total acid, 57). The blood was negative in every detail, including the Wassermann reaction. The urine was of normal specific gravity, free of albumin, sugar, and casts. Though the patient had complained of no intestinal symptoms, the feces, nevertheless, was found to contain numbers of *Entamoeba histolytica* cysts and showed a positive occult blood reaction. Physically, the patient presented a normal muscular development and an average weight was maintained. The chest organs exhibited no abnormalities. The blood-pressure measured 140/82. The abdomen presented a normal contour without distention and no sensitive areas were detected. No spasticity or sensitiveness was noted over the muscle groups complained of by the patient, and all the nerve reflexes were intact. The patient was first referred to a laryngologist, who reported a marked infection of both tonsils, which were submerged. Treatment of the entamebic bowel infection was immediately undertaken, and subsequently the tonsils were removed. Following this latter procedure the patient gained over 10 pounds in weight within two months and reported likewise complete relief from the previous muscular stiffness.

*Comment*—The finding of the *Entamoeba histolytica* in this case was in a way accidental during the course of a routine stool examination, and it was deemed essential that this infec-

tion be removed preceding tonsillectomy. The improvement that followed was probably the result of the eradication of the two foci of infection.

**Case X**—White female, aged twenty-four, single, born and reared in the rural districts of southern Louisiana. This patient came to the clinic with a history of having been sick for one year. The symptoms were those of an irritable stomach, upon a strongly neurotic background. She complained of sour belching, epigastric distention after eating, which was relieved by artificial vomiting or the taking of alkalies. She claimed to have an exaggerated sensation of hunger, but was afraid to eat because of the distress produced by eating. Her bowels moved once each day. The feces were semisolid in consistency. She felt tired upon arising in the morning and was able to do little housework. Her appearance was that of a decidedly undernourished individual with a small, bony frame, and marked pallor. The lungs were found to be normal. The heart was not enlarged, but a soft systolic blow was present along the left border of the sternum. The blood pressure was 112/71. Considerable tenderness was elicited upon palpation over the sigmoid. The abdominal wall was thin and gaseous distention of the intestinal coils was visible on inspection. The test breakfast revealed gastric subacidity without delay in motility. The blood-picture was that of a moderate secondary anemia. The Wassermann reaction was negative. The urine was also without noteworthy features. No ulceration in the lower bowel could be demonstrated by proctoscopic examination. In the small flakes of mucoid feces seen under the microscope vegetative types of *Entamoeba histolytica* were found. After treatment of this bowel infection the general condition of the patient improved markedly, including the gastric distress. The patient also gained in weight and it was believed a foundation was laid for the control of the neuropathic tendencies.

*Comment*—This case demonstrates the possibilities of a latent entamebic *histolytica* infection upon neuropathic individuals, which has often impressed itself upon us in our clinical records. It is always well to recall to mind that the so-called neurosthenic patients have potential organic lesions, and that they are also particularly susceptible to infections of various kinds. The removal of a chronic entamebic infection in such an individual frequently results in a restoration of the bodily energies and functions as a whole. In this connection, though no positive proof is forthcoming, it is probable that the pathogenic entamebæ produce toxic substances which effect a depressive influence upon the nervous centers in general.

## CLINIC OF DR CHAILLE JAMISON

### CHARITY HOSPITAL

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#### HEALED MILIARY TUBERCULOSIS OF THE LUNGS, WITH ANEURYSM OF THE ARCH OF THE AORTA

"HEMATOGENIC tuberculosis may be part and parcel of a generalized systemic dissemination of the infection, or may be confined to the lungs alone. As a rule, the tubercles are numerous but minute (miliary tuberculosis)"<sup>1</sup> Miliary tuberculosis of the lungs does not always end fatally, and the literature contains fairly numerous reports, based on both pathologic and clinical observations to support this view. Healing takes place by calcification or fibrosis, as a rule, though there seems to be some evidence that the lesions may heal and leave no recognizable scar.<sup>2</sup>

The diagnosis by physical signs and symptoms of acute pulmonary miliary tuberculosis is notoriously difficult, and in the healed state impossible. The roentgenogram of the chest, however, demonstrates a very striking picture. "When small nodules of uniform size with opacity suggesting calcification are uniformly scattered throughout a chest plate, healed miliary tuberculosis suggests itself, and this diagnosis has been made in several instances. Conclusive evidence in favor of this view has been lacking and there has been much difference of opinion concerning the interpretation of these plates"<sup>3</sup> Bierman<sup>4</sup>

<sup>1</sup> Adams and Nicholls, Principles of Pathology, vol 2, 1911, p 318

<sup>2</sup> Blaine, E S, Roentgenological Evidence of Apparently Healed Miliary Tuberculosis of the Lungs, Amer Jour Roentgol, 1924, 11, 233

<sup>3</sup> Opie, E L, The Diagnosis of Healed Miliary Tuberculosis, Amer Jour Roentgol, 1924, 11, 289

<sup>4</sup> Bierman, M I, Low Virulence in Miliary Tuberculosis, Minn Med, 1922, 5, 661



arbitrarily takes twenty-five lesions as the minimum which must be present in the lungs to justify the diagnosis of miliary tuberculosis

No case has been reported in the literature which shows not only the picture associated with healed miliary tuberculosis of the lung but also indubitable evidence of syphilis as evidenced, among other findings, of an aortic aneurysm. Syphilis may imitate any disease, and "healed gummas are to be distinguished



Fig 191 —Large aneurysm, with miliary tubercles throughout both lungs

from old tubercles and healed abscesses only with the greatest difficulty. Microscopically, they can only be distinguished from tubercles by the absence of the tubercle bacilli<sup>1</sup>

**Case History** —W. W., colored, age forty-seven years, a widower, from Houma, La., was admitted to the Charity Hospital May 24, 1925

<sup>1</sup> Adams and Nicholls, Principles of Pathology, vol. 2, 1911, p. 321

**Complaint** Pain in the precordial region and blindness

**Present Illness**—He was struck in the right eye by the limb of a tree fifteen years ago, and this accident was followed by blindness in that eye, in January, 1925 vision in the left eye began to dim, and has continued, until at the present time he can only distinguish light from darkness. On December 8, 1924 a severe pain occurred in the precordial region, this pain spread downward and to the right, it lasted only a short time. Since this attack he has had other less severe attacks of a like nature from time to time, these attacks have followed physical exertion. Shortness of breath occurred during



Fig 192 —Large aneurysm, with miliary tubercles throughout both lungs

these attacks. His feet and ankles have become slightly swollen only since admission to the hospital.

**Past History**—He has had measles, mumps, malaria, yellow fever, small-pox, and whooping cough. He had a urethral discharge in 1912, which lasted for three months; he denies any genital sores. A cataract operation was performed on the right eye several years ago.

**Family History**—Father died of "rheumatism" aged fifty-seven years, mother living and well at the age of seventy, of 5 brothers, 3 are living and well, 1 died in the war, of unknown cause, and the other lost his mind and subsequently died. 1 sister died at childbirth, the other is living and well.

The only member of the family who had tuberculosis was an uncle who died of this disease. The patient has 1 living child (legitimate) and 1 (illegitimate), his wife has had three miscarriages.

*Habits*—He has been a hard worker all of his life, and is a moderate user of alcoholics and tobacco.

*Physical Examination*—The patient was a well-developed, poorly nourished mulatto (light yellow), tending to the Caucasian rather than the negroid type, he was lying in bed, apparently comfortable, and taking an intelligent interest in his surroundings. The temperature was 98° F, pulse 107, regular and of good volume, respirations 24, the head was well developed, with a good growth of hair, the anterior temporal arteries were tortuous and distended, the malar bones were very prominent, with depressions where the teeth should be supporting the cheeks, his right eye was slightly exophthalmic, and there were no movements. The conjunctiva was red and inflamed, the cornea was opaque, the pupil was dimly observed as a fixed halo, the left eye was apparently normal, the pupil of the left eye reacted to light and distance. The thyroid was slightly enlarged, the blood vessels in the neck showed marked pulsations.

*Thorax*—The chest was well formed, rather undernourished, and of the asthenic type. There was a tendency to a barrel shape. The lower ribs were flared out, the clavicles were prominent, as was also the angle of Louis. The supraclavicular fossæ were depressed, the right more so than the left. There was an extensive pulsation in the second interspace, on the right, extending from the median line to the midclavicular line, this pulsation seemed to extend below the right clavicle. There was a marked pulsation in the supra-sternal notch. The apex beat was in the fifth interspace inside the midclavicular line. The expansion of the thorax was free and equal. Palpation confirmed inspection so far as the impulses were concerned. They were synchronous with the apex-beat. There were no thrills. Vocal fremitus was normal throughout the chest.

*Percussion*—A large area of dulness was found below the sternum in its upper part, extending on the right side from the lower border of the first rib to the upper border of the third rib, 5 cm from the edge of the sternum. On the left side this area began at the lower border of the first rib, 6 cm from the edge of the sternum, and extended down into cardiac dulness. The left border of the heart was 10 cm and the right border 4.5 cm from the midline of the sternum. Krong's isthmus was 6 cm on each side. The lower border of the right lung in the midclavicular line was at the lower border of the fifth rib, with an excursion of 3 cm in the axillary line, at the seventh interspace, with an excursion of 2 cm, in the scapular line, at the tenth rib, with an excursion of 2 cm. The lower border of the left lung at the midclavicular line was at the lower border of the fifth rib, with an excursion of 2 cm, in the axillary line, at the eighth rib, with an excursion of 3 cm, in the scapular line at the eleventh interspace, with an excursion of 2.5 cm. There was normal resonance to percussion throughout both lungs except in the interscapular region opposite the second, third, and fourth vertebræ, where resonance was impaired. Vocal fremitus was normal throughout. On auscultation, no râles were heard and the breath sounds seemed normal. There was

a harsh systolic murmur, best heard at the aortic area, and transmitted upward. There was a soft systolic murmur at the apex, which was not transmitted. The second aortic sound was accentuated.

The peripheral arteries were hardened to the touch. The blood-pressure was the same in both arms, systolic 118, diastolic 70.

The abdomen presented nothing of note. The external genitals appeared normal and there were no scars. The patella reflexes were lively and equal, and there was no Romberg sign.

*Laboratory Examinations*—Roentgenograms of the anteroposterior, lateral, and oblique views of chest: aneurysmal dilatation of entire arch of the aorta, opacities 2 to 3 mm in diameter, scattered throughout both lungs. Blood Wassermann strongly positive, spinal fluid negative. Total red blood-count, 3,700,000, total white blood-count, 8000. Small mononuclears, 19 per cent, eosinophils, 7 per cent, blood-cells resembling basophils, 7 per cent, neutrophils, 67 per cent. Anisocytosis, poikilocytes, and some nucleated red cells were present. Non-protein nitrogen, 28 mg per 100 c.c., urea nitrogen (est.), 14 mg per 100 c.c., creatinin, 1.1 mg per 100 c.c., uric acid, 3 mg per 100 c.c. Chlorids, quantity not sufficient. Blood-sugar, 85 mg per 100 c.c.

Urine was normal.

The intradermal tuberculin test was strongly positive.

*Course*—The patient's symptoms were markedly relieved by active antituberculous treatment. No treatment was given for the presumed tuberculous lesion, and, as a matter of fact, except for the Roentgen-ray findings, there was no evidence of tuberculosis, as the positive skin reaction cannot be regarded as definite evidence of tuberculosis in an adult patient, particularly if that patient be a negro. During the patient's stay in the hospital he had no cough and no sputum. He finally left the hospital symptomatically much improved.

*Discussion*—The pulmonary pathology, though extensive, gave neither physical signs nor symptoms, but was clearly shown by the roentgenogram. The aneurysm gave definite physical signs and also showed clearly on the plate. It must be borne in mind that plates of the chest always enlarge the structures shown, and that the opacities seen here are actually much smaller than they look. It is not unusual for an aneurysm of this size to give few or no symptoms. The presence of extensive and long-standing syphilis in this case is undoubted, as shown by the condition of the vascular system, the eyes, and the strong positive Wassermann, as well as the response to specific treatment. On the other hand, there is practically no evidence of tuberculosis, and, as Bierman<sup>1</sup> says, "Another

<sup>1</sup> Bierman, *Loc cit*

point of interest, and one not unexpected, is that none of the patients who showed the dissemination of the tuberculous colonies were colored, although their incidence was about 20 per cent. In them probably a wide-spread dissemination of tuberculous foci would result only in acute miliary tuberculosis with rapid exitus." It is easy for me to believe that the pulmonary lesions are syphilitic and not tuberculous. It is true that the condition did not improve, as shown by subsequent plates, but this was to be expected.

Even an autopsy would probably not be able to definitely settle the question, as Blaine quotes H. Gideon Wells as stating that, "A calcified tubercle even cannot be positively identified as a tuberculous lesion, however certain one may be that it is such."

Finally, I should like to point out that this case exemplifies the great importance of chest plates to the clinician, their routine use will often demonstrate pathology which cannot be shown by the physical examination.

## CLINIC OF DR RALPH HOPKINS

### CHARITY HOSPITAL

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#### THE STATUS OF SOME PROBLEMS IN LEPROSY

ALTHOUGH biblical description probably makes leprosy the oldest of recorded diseases, there remains today in the minds of the laity much confusion as to what the disease actually is, and an even greater lack of knowledge of how the problem of leprosy in a community should be handled. The mosaic rules for establishing a diagnosis rather clearly show that the disease now recognized as leprosy existed in biblical days, but that the Jews did not differentiate psoriasis, leukoderma, and some other skin diseases from leprosy. An interesting instance of confusion arising from the inclusion of other diseases in the biblical description of leprosy is Wallace's account of this disease in the sister of Ben Hur. The girl in this story, after exposure to contagion in a cell which had previously been occupied by a leper, was suspected of having contracted the disease when her mother also immured in the cell discovered on the palm of her hand what is described as a "scurf." Her suspicions aroused by this scaly spot, the mother leads the child to where a single ray of light falls on her face, and discovers that her eyebrows and hair have turned white. This is regarded as sufficient confirmation of the diagnosis of leprosy, though, as a matter of fact, a squamous eruption on the palm of the hand would not now be regarded as suspicious, and the hair of lepers is no more likely to turn gray than that of other individuals. Not infrequently in communities where leprosy is prevalent the traditional "white spot" still excites suspicion. I can recall being questioned by alarmed acquaintances concerning patients presenting patches typical of leukoderma and not of leprosy origin. The

laws laid down in Leviticus for the segregation of lepers indicate strong conviction of the danger of infection, the leper himself was unclean, contacts were unclean until purified, domiciles were unclean and in certain instances to be destroyed, and all engaging in the destruction of unclean houses also were unclean until purified. It may be that the great dread of leprosy and the exaggerated fear of its communicability entertained today in many communities is traditional from biblical days. The stoning of lepers in Palestine has seen an aftermath throughout the world.

Popular misconceptions about leprosy cannot be said to be due entirely to lack of interest on the part of the public, but rather to conflicting medical reports that reach the public concerning almost all its most important problems. The public reads that "the dread disease" has at last yielded to treatment, only to learn subsequently that the new specific has failed in the hands of other observers. While the federal government establishes an institution for the segregation of lepers, the state-ment is authoritatively made in New York that in a general hospital in that community lepers have not been a menace to those with whom they came in contact. The multiplicity of these honestly expressed contradictions is evidence of many unsolved problems. The purpose of this paper is a consideration of some phases of these problems coupled with a narrative of specific instances whose interpretation may add evidence or which may show how far their solution has progressed.

As early as 636 A. D. lazarettos were established in Italy.<sup>1</sup> In the tenth century England and Scotland were afflicted. In the eleventh and twelfth centuries during the crusades the disease spread all over Europe. At the time of the death of Louis VIII (1226) it is estimated by Leloir<sup>2</sup> that there were 19,000 leprosarina in Europe and 2000 in France alone. Under this enforced control the disease survived only in a few isolated districts, and from the fifteenth to the seventeenth century grad-

<sup>1</sup> Dyer, *American System of Practice of Medicine*, Loomis-Thompson, vol. II, p. 921.

<sup>2</sup> Leloir, *Traité de la lèpre*, Paris, 1885.

ually disappeared from the greater part of Europe to appear later in the colonies of the Americas and the islands of the Pacific and Indian Oceans

**Etiology**—The distribution of leprosy in the United States includes all the states except Idaho, Utah, Delaware, Maine, New Hampshire Vermont, and Tennessee Cases have been admitted to the National Leprosarium from all the states except those named In the gulf states the disease is recognized as being indigenous, while in others it is a moot question as to whether or not conditions permit its spread From some states only sporadic or imported cases have been admitted

Hansen's bacillus is generally recognized as the cause of leprosy With regard to the cultivation of the bacillus Castellani states that there are three views "1 That it has never been cultivated 2 That it can be cultivated as a streptothrix or nocardia 3 That it can be cultivated as a bacillus" He believes that the first view is the most generally accepted, while Bordoni-Uffreduzzi, Babes, Rost, Kedrowsky, Shiga, Hewlett, Bayon, Johnston, and others believe that it can be cultivated as a streptothrix, and Clegg, Duval, and still others hold that it can be cultivated as a bacillus Inoculation of animals has been only partly successful, and the results in human beings even more doubtful.

Light or temperature, or both, may have an influence on the development of leprosy skin lesions An evidence in support of this hypothesis is the marked tendency of nodules and infiltrated patches to occur on exposed rather than covered surfaces of the body In the typical advanced case of skin leprosy the distribution of lesions on the head shows this preference to a remarkable degree On the forehead the lesions, which often are over  $\frac{1}{4}$  inch in thickness, mass in a deeply infiltrated or nodular patch The upper border of this infiltrated mass is curiously margined, the line of demarcation closely follows the border of the scalp and is so sharply defined that a narrow band, quite even in width, of normal skin often shows at the juncture of skin and scalp The scalp is free of lesions unless entirely or partially bald, in which case infiltrated macules may



be found in the areas denuded of hair. It may be said in passing that the leper is not more prone to baldness of the scalp than the average individual. It is also worthy of observation that hair is not found growing on old leprous lesions on the hairy regions of the face. When a leprous patch or group of nodules invade the supra-orbital regions the eyebrows fall. The same is usually true in regard to the bearded region. The disfiguring eruption noted on the forehead is found also on other parts of the face, with the notable exception of the more protected orbital region. Often in cases so disfigured that they bear but slight resemblance to their former selves the region of the eyes stands out strikingly free of eruption. If the eyelids become involved, as the case progresses, the less protected parts are more liable to show the first lesions. It is along the eyelid borders that infiltration commences and the remaining more protected parts of the eyelids may be free even when the border has been involved sufficiently to cause complete loss of eyelashes. The enlargement of the ears long recognized as an important diagnostic sign of leprosy, is notably in conformity with the rule that exposed surfaces suffer most. The extension of the patch downward on the neck often presents the same sharply defined margin at its lower border which may coincide with the region over which the collar band is worn. In a few cases with thin necks and prominent Adam's apple a triangular area free of lesions has been seen in the protected part between the lower jaw and the larynx. In some cases the trunk is free and in many there is surprisingly little eruption in comparison with the extensive and deep lesions found on the face. On the dorsal surface of the hands there are more lesions than on the palmar. It is not intended that it should be inferred that the distribution of leprous lesions is limited to the exposed surfaces of the body nor that these regions are the sole habitat of the bacillus. Indeed, the bacillus of Hansen has been found in almost every organ of the body, and almost any surface of the trunk or limbs may present lesions unmistakably characteristic of leprosy. It may, however, be inferred that leprous lesions exhibit at least a preference for exposed surfaces and that the most fully developed nodular

lesions are more likely to be found on these surfaces than on the trunk. Moreover, the macular eruption found on the trunk does not, as a rule, show the same abundance of organisms as do the nodules found on the head. Light and temperature may not directly favor growth of the bacillus of Hansen. There is no direct evidence of this, but tissue changes may take place as a result of their action favorable to the growth of the organism.

In Louisiana, in which there is a large negro population, the incidence of leprosy, judged by the number of admissions to the Lepers' Home, is far less among negroes than among whites. The number of negro admissions in proportion to the negro population was much less than the number of white admissions in proportion to the white population. It cannot be said that the Louisiana law for the isolation of lepers has been less rigidly enforced in the case of negroes than it has been in the case of whites, the contrary is more likely to be true. Conditions favorable to the spread of the disease prevail more in the negro than in the white population. Is the conclusion to be drawn that the American negro has a greater natural or acquired immunity than his white neighbor? If the answer be in the affirmative it must be conceded that the American negro is an exception to most dark-skinned races in other countries.

The numerical preponderance of men over women in leprosanaria is a striking fact, and where large numbers are congregated the almost exact ratio of 2 males to 1 female is maintained. No satisfactory explanation has been offered for this curious fact. From *a priori* reasoning one would expect that the more gregarious male, in consequence of greater possible contacts, would be more liable to infection, but the large number of cases found in single families argues strongly that casual contact is not a source of as great danger as the prolonged and intimate association found in the home. The women and girls living in houses with lepers are certainly exposed more than the men whose work necessitates longer periods of absence from home. Possibly women have more natural immunity than men, and if this be true, it may some time serve as a clue to etiology and treatment.

Age and social status are of less etiologic importance than sex. After infancy and early childhood no age is exempt and, popular opinion to the contrary notwithstanding, leprosy is no respecter of persons. The Lepers' Home of Louisiana, where now is the National Leprosarium, has housed people of the highest social caste, and in the southern parts of the United States where leprosy is indigenous cases have occurred in the native born associated neither with poverty nor ignorance. Specific instances may not be mentioned, but it may be said that if wealth be taken as a criterion of social status, cases have come under observation that would far outrank the average successful business man.

Heredity as an etiologic factor in leprosy is not generally regarded as of importance, children born of leprous parents in Molokai have not only shown no evidences of leprosy at the time of their birth but also when promptly removed from their parents and kept under observation in asylums in Honolulu have not developed the disease in greater number than could be accounted for by the incidence of leprosy in the community as a whole. However, leprosy is notoriously a family disease occurring in many contemporary members and passing through successive generations. The explanation offered is that the long and intimate contact that prevails in the family relation affords sufficient opportunity for infection. Denny's statistics of 10,000 lepers in the Philippine Islands, and McCoy's, in the Hawaiian Islands, are surprisingly similar in the percentage of cases that gave a definite history of contact with a leper relative, 29 was the percentage for these islands, and in Louisiana the figure is even higher. Some years ago, when only patients from Louisiana were admitted to the Lepers' Home, a tabulation of the 232 inmates showed a percentage of about 15 as closely related as parent and child or brother and sister. Among these relatives was one family of 6 brothers and sisters, one family of 5 brothers and sisters, and one family of 4 sisters and their mother. At the time the tabulation was made there had been no instance of leprosy in both of a married couple. Denney's<sup>1</sup>

<sup>1</sup> Denney, Statistical Study of Leprosy in the Philippine Islands, Jour Amer Med Assoc, December 29, 1917, p 2171

and McCoy's tables also show a very much smaller occurrence in both of married couples than would be expected from the large number of blood relatives shown to have contracted the disease. The percentage of cases in which husband had infected wife or vice versa was only 1 per cent. In the light of present knowledge or rather, lack of knowledge of the method of transmission of the infection these figures are difficult to explain if the general assumption that heredity is unimportant be admitted. It must be conceded that leprosy is not directly transmitted from parent to child, but the author is among those who would attribute to heredity an importance in so far as predisposition is concerned. Granting an inherited diminished resistance and adding to this factor what may be regarded as ideal conditions for transmission, infection of blood relatives can be explained, while husband or wife may escape because of a natural inherited immunity. It is quite possible that predisposition is rare and that what has long been called "a taint of leprosy" in a family means merely an unusual and hereditary lack of resistance.

**Epidemiology**—That leprosy is a communicable disease is the view of most writers whose observations have been made in countries where leprosy is indigenous. However, in other sections leprosy does not seem to spread, and we have the statement of Fordyce and Wise<sup>1</sup> that for the past thirty years patients have been admitted to one of the large city hospitals, that many of these patients had open lesions, that they occupied beds in the wards in close proximity with other patients, that several were inmates of the hospital for years, and have there died, yet no case of contagion has been observed under these conditions. Fordyce and Wise further state that while the proof of the contagiousness of leprosy is incontestable, it is only mildly contagious.

The factors determining the communicability of the disease remain unknown quantities. One requisite seems to be long and intimate contact, but this alone does not seem to be sufficient. The author has previously suggested that an inheritable lack

<sup>1</sup> Arch. Dermat. and Syph., 1920, 2, 280

of resistance added to the conditions believed to be most favorable may offer an explanation for the large number of relatives infected and the very few instances of conjugal transmission. This view is further supported by the small number of instances in which attendants at hospitals for the care of leprosy have contracted the disease. The assumption that the average individual possessed a natural immunity would explain the escape from contagion of those exposed even under most favorable conditions for transmission.

The incubation period of leprosy has not been definitely established. It has been variously estimated as from a few weeks to forty years. Animal inoculation, having been only partially successful, has afforded but little information, and the result, one case of successful human experimentation, has been questioned because of the subject's having lived under conditions which did not preclude the possibility of his having contracted the disease in a natural way. This case, Keanu, a Hawaiian, was inoculated in 1884 by Arning, and developed in six months a leprous tubercle at the site of inoculation and in three years presented a well-marked case of leprosy. Keanu's son, nephew, and cousin were lepers, and from this circumstance has arisen the doubt as to whether Arning's inoculation was the cause responsible for infection. One case has come under the author's observation in which the history gives a fairly probable incubation period.

There were admitted to the Lepers' Home in 1895, 4 sisters, and in 1902 an adopted daughter of one of these sisters. It is the history of the adopted daughter that is of interest. The child, who was not a relative, was adopted early in life and lived with the adopting mother until 1895, at which time the mother went to the home. The mother had shown signs of leprosy during five years previous to her admission and had been nursed by the daughter. The girl, up to the time of the departure of her mother, had shown no evidence of leprosy, and after the mother had gone lived in a family in which there was no leprosy. She continued in good health until the latter part of the year 1901, when a typical macular eruption appeared, and in the

course of three or four months she was advised to go to the home. The period of her exposure was during her residence with her adopted mother from 1890 to 1895. Subsequent to 1895 the girl came in contact with no leprosy and, to the best of her knowledge, saw none. The probability is that she was infected during her residence with her mother, which would make an incubation period of at least six years. This estimate of six years tallies fairly well with incubation periods determined by other observers.

**Curability of Leprosy**—On December 6, 1904 the first patient was discharged as "cured" from the Lepers' Home of Louisiana. The case was that of a boy admitted October 16, 1902, with a characteristic leprous macular eruption. During the two years that he remained in the institution he was given systematic treatment with large doses of chaulmoogra oil by oral administration. His improvement was rapid and continuous, and some time before his discharge no vestige of the disease could be found. The author, in consultation with Dr. Isadore Dyer, assumed responsibility for his discharge and he was recorded "cured." On June 6, 1909 he was readmitted to the home presenting again unmistakable evidences of leprosy. He died November 3, 1910 of pulmonary tuberculosis without having shown any improvement in his leprous condition. In addition to this case 47 others have been discharged up to the present time. Of these, 9 have relapsed and been readmitted. It may be said that as time has elapsed the period of observation between disappearance of symptoms and discharge has been lengthened. It may also be stated that patients are not so boldly recorded as "cured." The regulations now governing the discharge of patients at the National Leprosarium require that a patient found no longer to be bacterioscopically a leper shall be examined by a board of 3 medical officers, who, if they consider the disease arrested or latent, may keep the patient under observation for six months, during which time bacterioscopic and physical examinations are made not less frequently than once each month. If during this six-month period no evidence of relapse is found the patient is removed to that portion of the reservation set aside for special

observation purposes and examined physically and bacteroscopically not less frequently than once each month for a period of one year, after which, in the absence of contraindicating findings, the board may recommend the discharge of the patients on probation as either "cured," "arrested," or "latent," and "no longer a menace to the public health." Observation of patients after discharge is also provided for in the regulations. Experience has disclosed no absolute criterion for adjudging a leper cured, frequent examinations and a long period of observation of those apparently cured are the greatest factors of safety. Clinical freedom of symptoms and a few negative microscopic findings cannot be taken as evidence of a "cure."

**Conclusion**—In conclusion I would express the conviction that cases of leprosy should be isolated, and that isolation is best effected in an institution devoted to the care of lepers. This conviction is the result of having seen during the last twenty years cases multiply in families to the extent of including all the sons and daughters. The occurrence of leprosy in a family is always a tragedy and isolation a hardship, but the hardship of separation from home and family is better than a multiplication of the tragedy.

# CLINIC OF DR LEON J MENVILLE

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### THE MEDICAL ASPECT OF NON-TRAUMATIC DIAPHRAGMATIC HERNIA. REPORT OF A CASE SITUATED ON THE RIGHT SIDE, ANTERIORLY

THE subject of non-traumatic diaphragmatic hernia may appear primarily more of surgical rather than of medical interest. It must be appreciated, however, that the herniation into the thoracic cavity of certain abdominal viscera, especially the stomach and intestinal coils, presents itself at first with a syndrome indicative of some internal medical condition. The pain and digestive disturbances often suggest gastric or duodenal ulcer. The invasion of the thoracic cavity may produce cardiac or other disturbances which gives the impression of some medical pathology inside the thoracic cage.

This condition may likewise appear as one of interest because of its unique character. With our improved facilities of radiography, however, the medical literature demonstrates that this rather obscure condition is apparently increasing. This is due to the fact that diaphragmatic hernias are now more frequently diagnosed in the living case. While early literature recounts a large number of cases observed at postmortem or occasionally at operation, its recognition *in vivo* before the employment of the x-ray as a diagnostic aid was almost unknown. In this manner it can be seen that it is of importance to include knowledge of this subject in our armamentarium of medical diagnosis.

According to Richard,<sup>1</sup> the first case of congenital diaphragmatic hernia was reported by Reverius in 1669. In 1724 Stehelinus<sup>2</sup> reported a case in which postmortem examination re-



vealed the stomach in the chest cavity, having passed through the diaphragm Richard states that Thoma and Grosser found reported in the medical literature 233 cases of non-traumatic diaphragmatic hernias up to the year 1900 These cases included false, true, and esophageal hernias, 175 of these cases were on the left side, 42 on the right, 8 were esophageal hernias, and 8 diaphragmatic eventrations Of this number, 12 were anterior, 6 on the left side and 6 on the right, 83 were central, of which 63 were on the left and 20 on the right side, including both true and false hernias, 19 cases were posterior, 18 of these were on the left and 1 on the right, including both true and false hernias Richard has tabulated the literature from 1900 to 1923, in which 135 cases of non-traumatic hernias were reported, 82 of these cases were on the left, 33 on the right, and 20 were esophageal hernias There were 12 anteriorly situated, 42 posteriorly, and 21 centrally These reports included the newborn, children, and adults

Giffin<sup>3</sup> in 1912 collected in the literature 650 cases of all forms of diaphragmatic hernias up to that date Struppler<sup>4</sup> collected 500 cases in 1901, including all types of diaphragmatic hernias, 107 cases have been found since then Most of these were either congenital hernias of babies or symptomless hernias discovered at autopsy Seibert,<sup>5</sup> in his review of the literature of this subject in 1916, found 252 cases Carmen<sup>6</sup> makes the statement that approximately 1200 cases of diaphragmatic hernias are on record up to 1924 The condition has been found in 20 patients in the Mayo Clinic, an incident of 1 in practically every 18,000 patients examined

While the number of cases of non-traumatic diaphragmatic hernias reported in the early literature is quite large, it is noteworthy that such diagnoses were made at postmortem or occasionally in the operating room Hedblom<sup>7</sup> states that Nauman in 1888 was perhaps the first to diagnose this condition during life and the first to perform an operation for such a condition This was before the advent of the x-ray as a facility in medical diagnosis Up to 1912 Giffin<sup>3</sup> reports that there were about 15 cases diagnosed during life Brietner<sup>8</sup> in 1921 states that

about 44 cases had been clinically diagnosed, only 6 of these cases were diagnosed without the x-ray. It is evident from these observations upon the literature that since the employment and with the improved efficiency of the x-ray in diagnostic medicine the diagnosis of non-traumatic diaphragmatic hernia during life is becoming more and more frequent. As the x-ray was only discovered in 1895, it can be appreciated that its application along such lines was several years later.

Dissertations upon the embryology, anatomy, and pathology of diaphragmatic hernias are reported by Sailer and Rhein,<sup>9</sup> Struppler,<sup>4</sup> Koniger,<sup>10</sup> Beltz<sup>11</sup> and Becker<sup>12</sup>

A diaphragmatic hernia is one in which herniation has occurred through the diaphragm from the abdomen, either through a congenital or acquired opening. This herniated mass may consist of various portions of the abdominal viscera. In the protrusion through the diaphragm it will most likely possess a peritoneal covering and a tunic of diaphragmatic pleura. Such a form of hernia constitutes a true diaphragmatic hernia. It is possible, however, for such protrusion to occur through trauma wherein the abdominal viscera may protrude through the artificial opening into the thoracic cavity without a definite hernial sac.

In regard to the definition of diaphragmatic hernia Richard<sup>1</sup> states "that the term 'diaphragmatic hernia,' according to many authorities, should be confined to those instances in which the abdominal viscera are inclosed in a sac composed of all, or at least one, of the component layers of the diaphragm. There are many writers who do not agree with this statement, claiming that 90 per cent of diaphragmatic hernias have no sac."

**Classification** — Richard's classification combines the essential features of this form of hernia in the following manner

- 1 True hernias (those with hernial sac)
  - (a) Congenital (present at birth)
  - (b) Acquired Through the natural opening (mostly esophageal)
  - (c) Elsewhere (traumatic or non-traumatic)

## 2 False hernias (those without sac)

## (a) Congenital

## (b) Acquired (all traumatic)

## 3 Eventration of the diaphragm

This classification does not differentiate between those cases in which a congenital weakness may have been present at birth and those in which the hernia did not manifest itself until later in life

**Etiology.**—In considering the cause of diaphragmatic hernias the same salient factors are involved as for hernias occurring elsewhere. These factors are divided into traumatic or acquired and congenital. As regards trauma as a factor, this type has appeared in the literature to a large extent during the last decade because of the fearful injuries inflicted through the modern wars, and especially due to the ravaging effect of modern war implements. Congenital defects, as is well known, have always played a considerable rôle in the formation of spontaneous hernias. Such congenital defects continue through time in apparently the same proportion. Weakened tissue and incomplete closure of openings or tracts during developmental processes and the like forms a "*locus minoris resistentiæ*" through which viscera, especially under pressure, may protrude beyond their normal confines. In the instance of the diaphragm the posterior portion is usually the area in which nature is the most at fault, and a hiatus or weakening may remain which predisposes to herniation from the abdomen. Actual herniation may be found through such opening in the fetus, and these weakened or susceptible areas may continue for years before the gradual weakening or undue eversion may provoke the herniation.

**Situation**—It is of interest to note from Richard's article the many situations occupied by diaphragmatic hernia. "A consideration of any large number of reported cases of diaphragmatic hernias would lead one to believe that there is no portion of the diaphragm which is exempt and no natural opening which cannot, theoretically at least, serve as a point of weakness. As a matter of fact, these hernias fall into several distinct groups, some much more common than others, and there are

certain points which never are the site of herniation. Thus the aortic opening has never been known to contain a hernia, first, because this opening is, anatomically and developmentally, not in the diaphragm, but behind it, second, its ring is tendinous, not muscular, and attached closely to the vertebræ by the crura on each side. The aorta is occasionally included in the hernial opening, but this is the result of defect of the diaphragm on one side and not of any herniation through the aortic opening itself. Similarly, the quadrilateral foramen, through which passes the inferior vena cava, has never been found to be the site of hernia. The various hernial sites may be divided as follows: central, posterior, anterior, esophageal, and others. Any of the first three types may be right or left, the latter being much the more frequent."

**Diagnosis**—These cases are rarely suspected by the clinician. Dependent upon the degree of herniation and the structures herniated the symptomatology of the case may vary exceedingly. When a radiographic examination of the gastro-intestinal tract seems indicated, it is through this means that the diagnosis is usually made. A thorough x-ray examination, including fluoroscopic, skiagraphic, and barium enema, should make a positive diagnosis in a large percentage of cases of diaphragmatic hernia. It is Oden's opinion that a routine examination, including a fluoroscopic observation, is by far the surest method of making a definite diagnosis. In fact, with its use it would seem almost impossible that a case could remain unrecognized, regardless of the symptoms suggesting a hernia, and the definite diagnosis should rest upon the x-ray finding. If, in addition to the usual meal, a barium enema is also given, it is possible to obtain definite information as to the involvement of the colon.

I thoroughly agree with Carmen<sup>6</sup> when he says that (1) purely clinical diagnoses have seldom been made, (2) purely roentgenologic diagnoses have often been made, (3) in routine roentgenologic examination of the chest diaphragmatic hernia have often been overlooked, or mistaken for other conditions, and (4) the co-operation of clinician and roentgenologist has led to the best diagnostic results.

**Differential Diagnosis** —As mentioned previously, the symptomatology may present wide variation, according to the structures involved in the herniation. Among the numerous diagnoses that have been confused with this condition clinically may be enumerated (a) eventration of the diaphragm, (b) pneumothorax, (c) pneumothorax from rupture of the stomach, (d) hydropneumothorax, (e) temporary elevation of the diaphragm, (f) a large cavity in the lower lobe of the lungs, (g) subdiaphragmatic pyopneumothorax, (h) gall-bladder disease, (i) esophageal stenosis, (j) peptic ulcer. It must be appreciated, however, that these conditions are clinical confusing factors and are of no consideration from the standpoint of radiologic examination.

**Symptoms** —As viscera of different varieties may be incorporated within the hernial mass, it is evident that the same clinical phenomena will not be present in all cases. As a general rule, the stomach and colon are included, and one or both may be present in the pleural cavity. For this reason certain symptoms are usually demonstrated. Hunger is generally experienced, but the occurrence of epigastric pain upon eating usually interferes with the capacity to eat. Distress is occasioned because of a sense of suffocation and pressure upon the heart, causing a feeling of impending danger of death. Unless vomiting or gaseous eructations occurs at this time, these symptoms become aggravated. A spasm of the diaphragm at the opening may seriously impede vomiting.

In view of the fact that similar observations have been noted in so many cases reported in the literature, it is reasonable to ascribe epigastric pain directly after eating, inability to take quantities of food, a sense of smothering or precordial pain and distress, and inability to vomit or belch during an attack, as cardinal signs which point toward the existence of a diaphragmatic hernia.

**Prognosis and Treatment** —It is said that about 15 per cent of diaphragmatic hernias result in strangulation, which augments the seriousness of the prognosis. Inasmuch as large quantities of food or liquids have been the cause of strangulation,

the medical directions consist of more frequent and smaller meals and symptomatic treatment. Surgery is, of course, the treatment of choice and, if successful, may result in a complete cure. In strangulation of the hernia surgery is imperative or death will rapidly follow.

The case of non-traumatic diaphragmatic hernia of part of the transverse colon herein reported is interesting because of its location on the right side and its anterior situation, in addi-



Fig. 193 — Normal stomach. Duodenal cap is not visualized.

tion to the fact that it was diagnosed during life. While it is realized that such cases are infrequently encountered, a familiarity with its clinical and radiologic manifestations may be the means of diagnosis when such a condition exists. It is for this reason that the subject has been deemed worthy of presentation.

**Case Report.—History** —The patient is a man aged forty-one, he was first seen in March, 1924. Although very thin, he had been in perfect health

up to four months prior to that time. He complained of severe griping pains in the pit of the stomach three to four hours after meals. Occasionally, this pain would come on during the night and enemata were required to bring about relief. There was some heaviness and infrequent nausea after eating, but never any vomiting. His appetite continued good. The bowels would not move for two or three days, after which time he would have a copious movement without the use of laxatives.

*Past History*—He has always been a hard worker. There had been no serious illness. He does not smoke or drink. The patient is married two



Fig 194—Plate of the twenty-four-hour barium meal, by radiographic examination, showing the proximal end of the transverse colon above the right diaphragm, and point of constriction.

years and has no children. No history of any accident or trauma of any sort can be obtained.

*Physical Examination*—The patient is very much undernourished, weighing 110 pounds, and his growth is stunted. The palate is highly arched. The teeth show a severe pyorrhea and evidences of oral sepsis are present. The posterior cervical, left epitrochlear, and inguinal glands are enlarged. The heart and lung show no abnormalities. The blood-pressure is systolic 154, diastolic 65. The abdomen is very thin and presents a right inguinal

hernia. Palpation of the abdomen elicits a sensitive spot in the epigastrium just beneath the xiphoid cartilage. The urinalysis is negative. The stool is soft and does not contain any occult blood. The patient would not permit passage of gastric tube.

**Roentgenologic Examination**—By means of the barium meal test a gastro-intestinal examination was carried out and the following data was obtained:

**Esophagus** negative

**Stomach** Position somewhat high for his build (asthenic), size, shape, peristalsis, and flexibility normal, mobility is somewhat restricted at the



Fig 195—Plate of the twenty-four-hour barium meal, by radiographic examination, showing the proximal end of the transverse colon above the right diaphragm, and point of constriction.

pyloric end of the stomach, but this structure is negative for any evidence of organic disease.

**Duodenum** Incompletely filled and at no time was the duodenal cap completely visualized. Appearance of the first portion of the duodenum would suggest adhesion rather than ulcer (Fig 193).

**Colon** Twenty-four-hour examination shows some of the barium meal in the cecum, and the proximal end of the transverse colon above the right diaphragm (Figs 194, 195).

Appendix not visualized



A barium enema was given the patient. The enema entered the colon without any difficulty until it reached the proximal end of the transverse colon, where the flow of the fluid stopped for a moment and then streamed over the right diaphragm. This was followed by a short retardation in the flow of the barium mixture, showing at this point a narrowing of the lumen of the colon due to a constriction of the colon in or near the opening in the diaphragm (Figs 196, 197).

The rest of the colon filled normally. A lateral skiagraph was made to locate the situation of the hernia, the result of which proved it to be anteriorly situated (Fig 198).



Fig 196—Barium enema, showing part of the transverse colon above right diaphragm (anteroposterior view)

A roentgenogram of the chest was also made, and demonstrated clearly the hernial sac in the lower right chest just above the diaphragm (Fig 199).

*Diagnosis*—Right sided non traumatic diaphragmatic hernia of the proximal end of the transverse colon, anteriorly situated

**Discussion and Summary**—Of recent years the diagnosis of non-traumatic diaphragmatic hernias is apparently more frequent in the living case. It is, of course, unlikely that the

actual occurrence of this condition has increased, and it is evident therefore, that the increase in clinical diagnosis is attributable to the radiologic facilities that have come into use. As this clinical condition may simulate certain abdominal and pleural cavity diseases, it seems important that the knowledge of its existence should be borne in mind so that a proper diagnosis may be made.



Fig 197 —Barium enema, showing part of the transverse colon above right diaphragm (postero anterior view)

We find in the literature that diaphragmatic hernias are usually located on the left side, passing through the left diaphragm into the left thoracic cavity. However, we must keep in mind the occurrence at times of these hernias on the right side which are of the same medical interest. There are certain symptoms manifested by these patients that have a direct

bearing upon the condition. In this manner, if the physician is so situated that radiologic facilities are not available at the time of examination, it is possible that the history of the case together with a careful physical examination may suggest non-traumatic diaphragmatic hernia. For the absolute diagnosis, however, the subsequent radiologic examination is essential.



Fig 198—Lateral view of barium enema, showing the hernia situated anteriorly

While but few diaphragmatic hernias have been diagnosed clinically, the Roentgen diagnosis is usually a simple matter. Certain difficulties are occasionally encountered even in the diagnosis with the Roentgen ray. These are especially apt to occur during the first examination. The following factors have been enumerated by Carmen<sup>6</sup> as the cause for such failures

(a) That diaphragmatic hernia may develop as a late sequel to a paradiaphragmatic purulent process, (b) that spontaneous reduction may occur, (c) that only one of a double hernia may be demonstrated roentgenologically, and (d) that the opaque medium may not pass through the diaphragm opening because of strangulation or on account of the patient's position during the examination. In cases when the solid viscera only form the



Fig 199 —Plate of chest, showing hernial sac on the right side and above the diaphragm

hernia contents it is obvious in such cases that the oral and rectal administration of the bariumized fluid will not reveal the hernia.

A Roentgen ray of the chest, as is usually done in a routine examination, will often fail to disclose the presence of signs of a diaphragmatic hernia. The only suggestive evidence obtainable in such an examination is the outline of the hernial sac and the displaced heart and large blood-vessels

An ordinary examination of the thoracic cavity with the x-ray is unreliable inasmuch as even the marking of the hernial sac may be confused with other pathologic conditions that may occur in the chest. However, such findings as enumerated should be followed by a barium meal, through which means a correct diagnosis is likely to be obtained. An important function of a Roentgen-ray examination in such cases is to ascertain the hernial opening, if possible, as such information will prove of great value to the surgeon.

Hedblom<sup>7</sup> reports in a series of 378 cases collected from the literature that the colon was found herniated in 37 cases and colon and omentum in 28. No mention is made as to whether they were located on the right or left side. In another series of 163 cases collected by the same author, 7 cases, or 2 per cent, were situated anteriorly. The side of their location was not specified. In this manner the unusual location and situation of the hernia herein reported can be realized.

The diagnosis of this case was made by a Roentgen-ray examination alone, as the patient refused operation. The case described is interesting in many ways, its location on the right side and its anterior situation are unusual. It is also interesting to note that up to four months previous to being examined the patient was in perfect health. This history of the case illustrates that the condition may exist for a period of time without any manifestation of its presence. It is evident that his symptoms developed when the constrictions in the colon occurred.

*Conclusion*—It may be stated that the subject of non-traumatic hernia is important inasmuch as its recognition is becoming more frequent and because it may present a varied symptomatology suggestive of other medical conditions from which, however, it can be definitely differentiated.

*Note*—This case was referred to me by Dr. D. N. Silverman for radiologic examination, and I wish to express my thanks for his courtesy in presenting me with the clinical data.

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# CLINIC OF DR FOSTER M. JOHNS

TULANE UNIVERSITY

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## THE TREATMENT OF CHRONIC AMEBIC DYSENTERY WITH STOVARSOL

It is very apparent to those of us who have treated amebic infections with stovarsol (acetylaminohydroxyphenylarsonic acid<sup>1</sup>) that we possess in this synthetic arsenical compound a truly specific amebicidal drug. The astonishing rapidity with which both vegetative and encysted amebas disappear from the stools coincident with the complete relief of dysenteric symptoms is not paralleled in my experience by any other specific therapeutic drug. On the other hand, the complete eradication of all amebas present in the lésions constitutes the problem upon which the ability to effect a permanent cure must be based. The pathology in severe amebic ulcerations shows the lesions in the submucosa of the colon and rectum to be masses of semi-necrotic tissue with only an occasional partly functioning blood-vessel, sinuses filled with enormous numbers of amebas extending sometimes for many millimeters into the healthy tissue beyond, and the thick border of epithelial cells of the mucosa ready to seal over the ulcer with the least cessation of amebic activity. In other words, our concept of this protozoa at present is that the parasite lives and reproduces entirely within the tissues, and, like other protozoan diseases, the ameba can lie semidormant for a considerable length of time when buried in apparently healed lesions. It has been our experience that patients contracting amebic dysentery who are diagnosed promptly and treated rigorously are comparatively easily cured,

<sup>1</sup> Johns, F. M., and Jamison, S. C., Jour Amer Med Assoc., 1925, 84, 1913



whereas the case of several years' duration relapses with great regularity, and is often pronounced incurable. If it takes several years of consistent treatment to arrest a syphilitic infection with two or three specific drugs, may it not take a considerable time for any specific medication to destroy all of the amebas in a grossly diseased and altered gut wall?

An interesting case showing the necessity for prolonged treatment and careful laboratory watching is the following

W A S, a white man twenty eight years of age, ice-man by trade, was suddenly seized with dysentery five years ago. A diagnosis of amebic dysentery was promptly made by a member of our staff and treatment with emetin instituted, resulting in a clinical cure. Ten months later another acute attack was treated. Eight months after this another attack was experienced, which was treated with emetin and followed by a course of 100 ipecac pills administered while in hospital. Relief for several months was obtained, and for the following three years there were only occasional periods during which he was free from symptoms.

On November 17, 1924 the patient was referred for experimental treatment with stovarsol. He had just received twenty-two daily injections of emetin, which had resulted in checking the stools to four or five daily. A soft fecal passage was examined and no cysts or vegetative amebas found. Proctoscopic examination revealed several large healing ulcers on the floor of the rectum from which numerous vegetative forms of *Endameba dysenteriae* were found in curettings.

Three 0.25-gm tablets of stovarsol by mouth daily (one-half hour before meals), to be continued for one week, was directed, with no change in diet or habits.

Complete relief from symptoms was observed by the patient on the third day of medication. Seven days after completing the stovarsol the stools were still normal and free from parasites. The week's course of stovarsol was repeated.

Twenty-nine days later dysentery began suddenly, with several bloody mucoid stools, griping, and abdominal pains. Proctoscopic examination showed the former large ulcers had healed and there were now numerous ulcerations of pinhead size scattered uniformly over the rectum and lower part of the colon. Fecal particles removed from the colon showed a few pre-cystic amebas. Bloody mucus from lesions contained numerous vegetative forms.

Stovarsol gave relief within twenty-four hours, and was continued in three 0.25-gm doses daily for seven days. Seven 0.065-gm (1 grain) daily doses of emetin were then administered, and this was followed by another week of stovarsol with three tablets daily.

For the following sixty-four days the patient remained entirely well. Four stool examinations failed to show any evidence of infection in the form of vegetative amebas (in warm stools) or cysts in centrifuged preparations.

(The centrifuge preparations of whole stool suspension when properly done not only averages the fecal mass, but achieves a 25 to 1 concentration of cysts.)

Seventeen days following the last stool examination an acute dysentery began, which within twenty-four hours had almost prostrated the patient, with continuous pain, griping, and passage of innumerable small bloody stools. Proctoscopic examination revealed three large ulcers in the rectum alone, which had apparently become necrotic underneath the mucosa and had suddenly broken through the epithelium.

Four 0.25-gm tablets of stovarsol daily were directed, to be continued for one week, to alternate by the week with two tablets daily, the entire course to continue thus for four weeks.

The patient reported that the acute symptoms had all disappeared within forty-eight hours and that the full month of medication had not only been completed without any symptoms of arsenic intoxication, but that he had gained a great deal of weight and felt in perfect health.

A stool and proctoscopic examination three weeks later failed to reveal any abnormality and another four weeks' course of stovarsol was instituted, which has just now been completed without any untoward symptoms.

**Discussion** —It is apparent from this and other cases that we have no means at present of determining the length of time necessary for a specific remedy to reach and destroy all of the parasites in a given case. Relapse may occur clinically, as dysentery, and sometimes with remarkable suddenness and severity, or in a more chronic form as shown by cysts, which presupposes small ulcerations in the cecum or upper part of the colon, or by the occurrence of liver abscess. Patients who show by clinical trial a tendency to relapse at intervals of several months should be kept under observation and periodically should be given interrupted courses of treatment to destroy such parasites as may have migrated or have been brought to within the zones of therapeutic effectiveness of the specific remedy. For the patient here presented we intend to continue alternating treatment and rest periods at monthly intervals for at least a year.



# CLINIC OF DR V J THACKER

## CHARITY HOSPITAL

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### THE HEART IN HYPERTHYROIDISM

UNTIL quite recently American medical literature contained only scattered and incomplete reports on this important subject. However, in the last two years "thyroid hearts" have been studied by a number of careful observers.

It is my purpose to present in a brief way the most widely accepted ideas and findings on certain phases of the subject, namely (1) The etiology or primary cause of the cardiac involvement; (2) the physiologic pathology and evolution of the stages of progressing cardiac involvement, (3) the clinical types of cardiac disease most frequently seen, with special reference to auricular fibrillation.

There is some difference of opinion as to the incidence of cardiac involvement. According to Hamilton<sup>1</sup> 65 per cent. of cases of hyperthyroidism are spared heart complications. Goodall<sup>2</sup> states that most cases of hyperthyroidism show some definite cardiac involvement. Willius and Boothby<sup>4</sup> claim that cardiac disease is not as common in these cases as is generally believed. Dameshek<sup>6</sup> concludes that an average figure would be around 25 per cent. This apparent discrepancy is dependent chiefly on the fact that the various observers differ as to just what constitutes cardiac involvement, some considering even tachycardia a symptom of cardiac change, while others have considered normal all cases except those short of actual heart failure.

Definite cardiac change occurs sufficiently frequent to be considered a definite clinical entity, Goodall<sup>3</sup> applying the name

"goiter heart" The name "thyrotoxic heart," which he also uses, or "the heart in hyperthyroidism," are more specific and appropriate names

1 We may now consider the question of the etiology or primary cause of the cardiac involvement It can be said from the start that the etiology of the thyrotoxic heart is still based more on theory than on fact

(a) The mechanical pressure theory is the oldest one and, according to it, changes are brought about by the pressure due to enlargement of the gland chiefly This pressure is exerted on the vessels and on the trachea, and by a rather complex mechanical explanation the supporters of this theory tried to explain the cardiac involvement Likewise there is another pressure theory in which pressure on the nerves to the heart causes its degeneration, but it has no proof These theories are quite inadequate, as not infrequently, even in severe cases, the thyroid gland is slightly and at times not appreciably enlarged Also one would expect as severe and often severer cardiac damage from the simple goiters because of their size and position

(b) The mechanical theory of increased metabolism, necessitating increased work by the heart with resultant fatigue of this organ, is considered an important factor by several observers Boas<sup>7</sup> in particular stresses this "overwork" theory and, in addition, mentions two additional factors which will be referred to later

(c) The toxic theory has recently come into favor By this is meant that the thyroid gland gives rise to a definite substance, be it increased thyroxin or an altered thyroxin, which poisons the myocardium Dameshek<sup>6</sup> considers this the important factor, and only by it can all the cardiac phenomena occurring in hyperthyroidism be explained This would naturally raise the question Are the cardiac changes and their mechanism of production the same in exophthalmic goiter with a supposedly altered secretion and in toxic adenoma with a high unregulated concentration of thyroxin? Further investigation is necessary along this line

2 The physiologic pathology and evolution of the stages of progressing cardiac involvement Willus<sup>5</sup> explains the production of cardiac damage as follows First, excess of thyroxin causes increased metabolism, increasing cardiac work as shown by acceleration of rate with increase in contraction amplitude and a greater volume outflow per beat, leading to hypertrophy with attendant dilatation, second, the effect of thyroxin on the tissues is cellular, so the effect on the myocardium is degeneration, associated with muscular fatigue, and one of two subsidiary reactions may occur (1) May remain rhythmic, but further hypertrophy and dilation occur and even heart failure, (2) arrhythmia may occur, usually auricular fibrillation Then, as a result, circulation of myocardium is diminished with increased loss of tonicity, favoring further dilation and hypertrophy, and ultimately heart failure

Goodall<sup>2</sup> traces the pathologic physiology in a not dissimilar way, briefly, as follows (1) Tachycardia, (2) myocardial exhaustion as a result of overaction over a long period, (3) atonia results from or follows above, with (4) resulting actual dilatation, then (5) myocardial exhaustion is replaced by degeneration with impaired conduction, (6) auricular fibrillation or arrhythmia develops, (7) heart failure and even death is the final outcome if the condition progresses sufficiently

The steps in the production of the cardiac damage are similarly expressed by the various writers It is chiefly on the subject of the relative importance of the mechanical and toxic influence wherein writers differ The majority include both factors—Willus,<sup>5</sup> Boothby,<sup>4</sup> Goodall,<sup>3</sup> and Bircher chiefly Dameshek<sup>6</sup> and Hashimoto<sup>8</sup> favor chiefly the toxic theory or factor Boas<sup>7</sup> favors the mechanical, but in summarizing says "that the mechanical factors overloading the heart make it more susceptible to secondary noxious substances" He also brings out additional factors overloading the heart, first, tremendous dilatation of the veins and arteries of the thyroid circuit flowing to the neck, thus increasing cardiac work, and second, heightened oxygen consumption and increased carbon dioxide elimination necessitating a 25 to 60 per cent increased flow of blood

The toxic theory, the most favored one, is supported by the pathologic examination of the heart at necropsy. Unfortunately, a great deal of work along this line has not been done. I will endeavor to review the essential lesions as have been found by various investigators. According to Boas<sup>7</sup> necropsy shows dilatation of both chambers, with fatty infiltration of heart muscle cells and in some small scar areas surrounded by a cellular infiltration. Goodpasture autopsied 2 cases and found patches of acute myocardial damage shown microscopically by hyalinization of some muscle-fibers and a peculiar fraying out of most others. The fibrils were thinner and more widely separated, as well as lighter staining at the center.

The largest series is that of the Mayo Clinic reported by Wilson<sup>9</sup> in which 21 cases came to autopsy. Some degree of hypertrophy was noted in 16. Histologically 18 showed apparently swollen fibers with indistinct striations and well-marked lipid changes. The general impression of the musculature was that of "weak muscle."

Hashimoto<sup>8</sup> studied the problem experimentally in animals. Histologically he found a lymphocytic infiltration between muscle-fibers and around blood-vessels in necropsy of human cases. Experimentally in animals by feeding them thyrotoxin he produced similar lesions to those found in human cases. These were briefly (1) Process was chiefly localized in interstitial tissues, the parenchymatous changes being less marked, (2) inflammatory changes were non-suppurative, (3) there was a tendency to form cell collections between muscle-fibers around blood-vessels. He concludes, as does Fahr,<sup>15</sup> that myocardial changes are not due solely to excessive mechanical strain, but to a circulating toxin which may have a direct action on cardiac muscle, and is responsible for degenerative and inflammatory changes found and which toxin might be found in thyroid substance itself. Fahr<sup>15</sup> raises the question as to why the heart is affected more than other organs, and he believes that mechanical strain predisposes the heart to the toxin. From the above findings at necropsy there is fairly definite evidence of toxic action of some kind affecting the myocardium, substantiating the toxic theory.

3 The types of disorders found in hyperthyroidism and the nature of thyrotoxic or goiter heart, with special reference to auricular fibrillation, will now be considered

Dameshek,<sup>6</sup> in his series of 141 cases of hyperthyroidism, regards 28.5 per cent under the title of damaged hearts. Willis and Boothby<sup>4</sup> state that about 20 per cent of their cases showed varying degrees of cardiac weakness, 2 per cent had serious cardiac disease. In Hamilton's<sup>11</sup> study of 900 cases 50 cases had heart failure of the congestive type. Tinker<sup>13</sup> states that myocardial insufficiency puts some patients in the "desperate risk" class as he describes it. Goodall<sup>2</sup> stresses the importance of the thyrotoxic heart. Dameshek<sup>6</sup> puts 23 of his 141 cases in the heart failure class. From the foregoing brief analysis of the findings and opinions of several observers who have given the subject special study the heart in hyperthyroidism is seen to be of considerable importance. In an appreciable percentage of cases the cardiac phenomena dominate the picture and demand energetic treatment.

How do the cardiac disorders manifest themselves in hyperthyroidism? One of the earliest signs of Graves' disease are attacks of palpitation paroxysmal in type and brought on often by excitement or other emotion. It is not a manifestation of cardiac damage, but rather is a sign of heightened irritability.

Tachycardia is the outstanding symptom of thyroid disease. It is not, according to most students of this problem, evidence of a damaged heart, but chiefly a response to the increased metabolism in this disease which necessitates an increased blood flow. Goodall<sup>2</sup> speaks of it as a physiologic tachycardia. In severe cases it reaches 180 or over beats per minute. So tachycardia itself is not a manifestation of cardiac disease. The result of long-continued tachycardia has been discussed in a previous section.

After a time in a certain number of cases arrhythmia develops, and this is usually auricular fibrillation. The association of and frequency of this disturbance of rhythm is stressed by most observers. Hamilton<sup>1</sup> considers it the first significant



heart complication Pardee<sup>10</sup> regards it as "the most dangerous effect of toxic goiter," and calls attention to its almost constant presence in heart failure in cases of hyperthyroidism, stating that all but one case of heart failure had auricular fibrillation. He further regards this arrhythmia of the persistent type as the common cause of heart failure. In Hamilton's<sup>1</sup> 50 cases of congestive heart failure, 39 had persistent fibrillation and 9 had fibrillation of the paroxysmal type. Willius<sup>4</sup> says that it occurs in about 22 per cent of cases, while Goodall says 20 per cent. Hamilton<sup>11</sup> further states that 10 per cent of cases have auricular fibrillation as a direct result of hyperthyroidism.

There are three types of fibrillation described: (1) The persistent or established fibrillation present in 8 per cent of Willius'<sup>4</sup> cases, 25 per cent of Dameshek's<sup>6</sup> damaged heart cases, and in 39 of Hamilton's<sup>1</sup> 50 cases of congestive heart failure. (2) Paroxysmal or intermittent fibrillation was present in 5 per cent of Willius' series, 9 of Dameshek's<sup>6</sup> damaged heart cases, 41 in number, and in 9 of Hamilton's 50 cases of congestive heart failure. (3) Willius also speaks of transient fibrillation occurring in 9 per cent of his series.

There are certain factors which seem to influence the incidence of fibrillation. It occurs almost entirely in cases of long duration or prolonged thyroid intoxication, usually after years rather than months. These cases, as a rule, first have a transient and paroxysmal fibrillation which, as the disease progresses and cardiac damage proceeds, becomes a persistent fibrillation. At times, however, in severe cases fibrillation may occur from the onset. Duration rather than intensity of intoxication seems to be, however, the dominant factor in production of auricular fibrillation. Age is also a factor, the incidence increasing with age. Hamilton<sup>12</sup> stresses this factor and that practically all cases over fifty years of age with heart damage, especially when failure develops have fibrillation. What, then, is the significance of auricular fibrillation in hyperthyroidism? Practically all cases of cardiac failure show it, and it may be present in cases in which heart failure has not occurred. It does not stand then absolutely for heart failure.

Persistent fibrillation indicates, according to Wilhus<sup>1</sup> and Boothby,<sup>4</sup> "severer cardiac damage" Goodall says it shows the myocardium is profoundly poisoned Dameshek<sup>6</sup> includes it as an important feature of damaged hearts Pardee<sup>10</sup> states that fibrillation "is the most dangerous effect of toxic goiter," and Hamilton<sup>1</sup> considers that it should be present to make a diagnosis of cardiac failure in this disease, and that its association with thyroid disease is a definite clinical fact

Other cardiac conditions are of minor importance and will be mentioned briefly Premature contractions, occurring in 14 per cent of cases according to Wilhus and Boothby,<sup>4</sup> are of little or no significance Paroxysmal tachycardia occurs in 1 per cent according to Wilhus and Boothby,<sup>4</sup> with no serious outcome Dameshek<sup>6</sup> reports 1 case of auricular flutter and 1 of auricular tachycardia in his series of 141 cases As to disturbances of conduction, Dameshek in the same series reports 2 cases of paroxysmal complete block and 2 of delayed conduction Wilhus and Boothby<sup>4</sup> reported 2 cases of sino-auricular block in 377 cases, and to which they attached little significance They had one case of serious delayed A-V conduction Goodall<sup>2</sup> says that impaired conduction shown by P R interval by the electrocardiogram frequently exceeds one-fifth of a second in cases of myocardial degeneration

Cardiac enlargement is present in cases showing cardiac damage Goodall<sup>3</sup> says that the Roentgen ray shows the heart typically rather large and horizontal with apex outside of the nipple line

All of Hamilton's<sup>14</sup> heart failure cases showed enlargement However enlargement is to be expected due to hypertrophy and dilatation

Murmurs are not at all diagnostic Systolic murmurs are frequent, while diastolic murmurs are seldom heard, and if present usually mean coexisting cardiac disease of another type The murmurs are usually due to dilation of the left ventricle with mitral incompetency and are heard chiefly at the apex and are of variable transmission They disappear when the disease is terminated

**Summary and Conclusion**—(1) As to the incidence of definite cardiac damage in hyperthyroidism, 25 per cent would be an average figure with severe cardiac damage in from 2 to 6 per cent, depending on the various series of cases considered

(2) In reference to the origin and production of cardiac damage in this disease the old mechanical pressure theory is no longer tenable. The toxic theory has been coming into favor, as it is the only theory that adequately explains all the cardiac phenomena occurring, as observed clinically as well as at necropsy. However, most observers consider the mechanical theory of increased metabolism, necessitating increased cardiac work an important factor, making the heart more susceptible to the thyrotoxic influence, this toxin arising from the thyroid gland, being either an increased secretion of thyroxin, an altered secretion, or both

(3) The steps in the production of cardiac damage are apparently as follows. Increased metabolism, increasing cardiac work as shown by tachycardia and increased output of blood, fatigue results and leads to hypertrophy and attendant dilatation and atonia. The toxic action comes into play, leading to degeneration in susceptible hearts. In time cardiac damage manifests itself by further dilatation and hypertrophy and even heart failure without arrhythmia, or, much more frequently, arrhythmia, usually auricular fibrillation, occurs usually with heart failure, most commonly of the congestive type

(4) The actual pathology found at necropsy seems to confirm the toxic theory, since degenerative and non-suppurative inflammatory lesions are rather constantly found and reported by various investigators

(5) Of the special disorders of the heart, auricular fibrillation is essentially the only important arrhythmia found. The constancy with which it is found in damaged hearts is striking. It usually means when of the established type, that the heart is rather seriously involved. Practically all cases of heart failure show it. Paroxysmal fibrillation is not as serious, but usually precedes the established type. Auricular fibrillation, then,

generally means that the heart is definitely damaged and failing. Furthermore, its presence further decreases cardiac efficiency and increases the strain on it, thus favoring further heart failure. In its production long duration of hyperthyroidism seems to predispose, as the incidence increases with age, and after fifty years of age fibrillation is an almost constant accompaniment of heart damage

(6) Other cardiac disorders are of minor importance and not characteristic or frequent

(7) Cardiac enlargement is present constantly in damaged hearts, both dilatation and varying degrees of hypertrophy accounting for it. Murmurs systolic in time occur, but are not diagnostic and are not due to valvular disease in uncomplicated cases, but to left ventricular dilatation with a relative valvular insufficiency

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# CLINIC OF DR C L ESHLEMAN

## TOURO INFIRMARY

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### LONG-STANDING HYPERTHYROIDISM WITH SPONTANEOUS SUBSIDENCE

**Case History**—This patient is an interesting thyroid case whom I have had under observation for fourteen years

She is a colored woman now fifty-seven years old. She has done no work for many years on account of her illness. She first came to me in this clinic in 1911 complaining of great nervousness, swelling of feet and legs, exophthalmos, and enlarged thyroid.

At that time she told me that her symptoms had first been noted eight years before (in 1903), apparently beginning with nervousness for many months following the shock of her husband's death. She then noted tremor of her fingers and was unable to thread a needle. Exophthalmos soon followed, and she was finally told by an oculist that she had exophthalmic goiter.

For four or five years she was under the treatment of a number of physicians. For instance, she was rested in bed at intervals and given sedatives and hypnotics and digitalis. About 1907 one physician treated her thyroid by Roentgen-ray exposures once or twice weekly for three months. About 1909 another physician gave her the serum then being advocated by Dr Rogers of New York. During this time she tells me she was nervous, had rapid heart action, lost much weight, and was swollen and short of breath on slight exertion. She had noted no immediate or striking benefit from any treatment.

When I saw her she was a slender, moderately emaciated mulatto weighing 122 pounds. She was very nervous and apprehensive. Tremor of fingers and bilateral exophthalmos was marked. The thyroid was moderately and symmetrically enlarged, involving both lobes and the isthmus, the circumference of her neck over the thyroid measuring 14 inches. The arteries and veins in her neck pulsated visibly. Precardia was prominent, heart enlarged to right and left, sounds were rapid and grossly irregular. A loud systolic murmur was transmitted to axilla, a few moist râles at both bases. Liver was four fingers below the costal arch and sensitive to pressure. Legs were edematous to the knees. Systolic blood-pressure 175. Urine showed a trace of albumin.

For several weeks during this attack of dilatation her condition was critical. She was orthopneic, coughed and expectorated whitish frothy mucus, either blood tinged or very bloody. With rest and digitalis she finally improved, but was never free of edema of the extremities.

From the time when I first saw her in 1911 until September, 1916 she was under constant observation. Various drugs were used, especially bromids, and neutral quinin hydrobromate in 15 gr doses daily. Chromium sulphate, 4 gr three times a day, was given for several months. No iodids were used at any time. I could see no improvement in the hyperthyroid condition directly resulting from any treatment. During these five years she frequently experienced periods when her heart weakness was so pronounced as to make me feel that she would not respond to rest and any kind of medication. She often remained in bed for months. Digitals was her

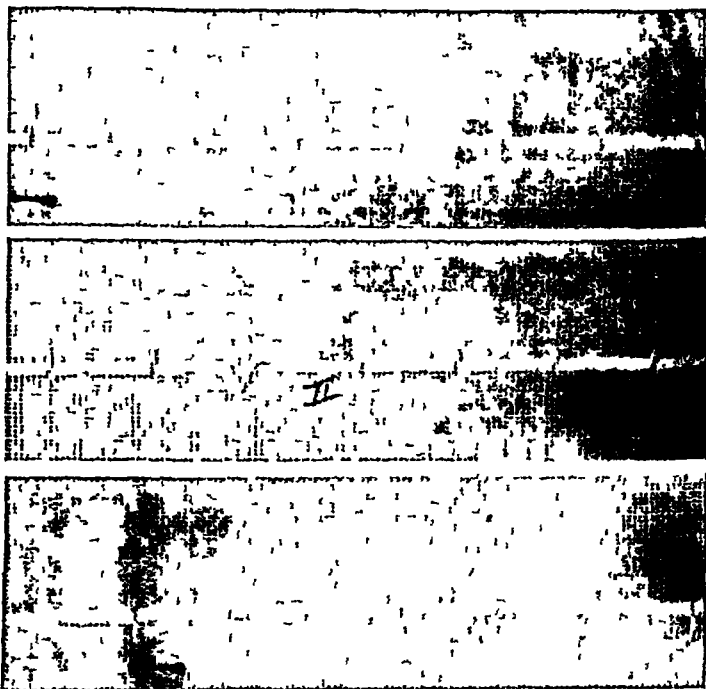


Fig 200—Electrocardiogram in patient with exophthalmic goiter, made in August, 1923, showing notably auricular fibrillation

mainstay. Surgery was not possible. Dr Matas and other surgeons who saw her considered any operative attempt at either ligation or thyroidectomy too great a risk.

From September, 1916 to January, 1918 she did not report to me, but no one else treated her. She took digitals when she needed it. She began to improve during this period, because when I saw her on the latter date a distinct change was noted. She had gained 40 pounds and the thyroid had so diminished as to be hardly noticeable, her neck measurement being 12½

inches She was still nervous, but not to the same extent Tremor varied, sometimes it was absent The exophthalmos was still very striking and the fibrillating auricles with edema of extremities still present From this time on she showed slow but steady improvement, her nervousness and tremor gradually diminishing Basal metabolic observations were now possible, and in May, 1921 the rate was plus 35 per cent, average pulse rate 96, weight 172 pounds In February, 1922 B M R. was plus 44.2 per cent, pulse rate 98, very irregular, weight 154 pounds Moderate edema of lower extremities still present Blood-pressure 178/100

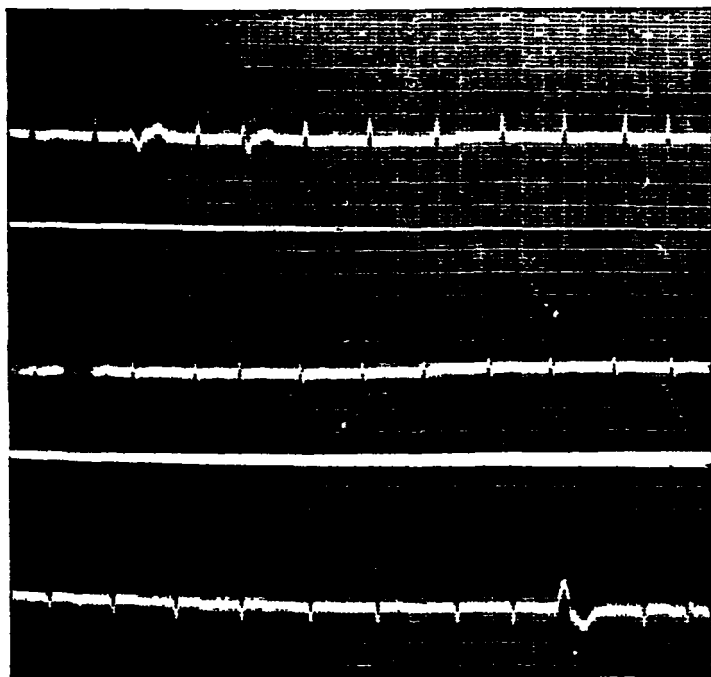


Fig 201—Electrocardiogram of patient made in 1925, again showing persistent fibrillation

By February, 1923 all thyroid symptoms were in the background, but she was in bed due to dyspnea, increased dropsy, and hemoptysis By the first of April she was much better, but soon relapsed, and was much worse on account of a right hydrothorax. Her condition was very grave and she was in bed three months By August she was comfortable and getting about, but a cardiogram (Fig 200) showed a severe myocarditis with auricular fibrillation, arborization, Q and S wave abnormalities, T wave diphasic, ventricular premature beats, ventricle rate 105



During 1924 she was in fair condition. In March, 1925 she again developed a right hydrothorax and 2 quarts of fluid was aspirated. In two months she was better and able to go out.

At the present writing she looks better than at any time since I first saw her. Her exophthalmos has largely subsided, but is still noticeable, and is the one thing which stamps her as having been once a hyperthyroid case. The upper lid follows the eyeball downward very readily. Convergence is good. No tremor is present and no nervousness noticeable. The thyroid has atrophied and cannot be considered enlarged. Heart is enormously enlarged, a loud systolic murmur still present. Pulse rate 79, a rare extrasystole present. Blood pressure 114/80. Lungs negative, abdomen negative. Liver normal in size, spleen not felt. Legs edematous only to the middle third, over which area the skin is greatly indurated and pigmented. B. M. R. plus 15 per cent. Electrocardiogram (Fig. 201) shows auricular rate 90, ventricular rate 90, auricular fibrillation, premature contraction from left ventricle, left ventricle preponderance.

**Discussion**—Looking back on the history of her case, you will note that the toxic symptoms associated with her thyroid dysfunction were prominent and serious from 1903 to 1916. Between 1916 and 1918 these symptoms began to abate, and she gained much weight with gradual diminution in the size of the gland, until at present she really is no longer a toxic thyroid, but merely a case of myocarditis able to carry on only greatly diminished activity. This is merely the residual damage of many years of thyroid intoxication, and she is now, at fifty-seven years, a chronic cardiac case.

I do not know why she did not die years ago. I cannot associate the improvement with any treatment. The Roentgen-ray exposures years ago may have started atrophic changes in the hyperplastic gland. Good results from Roentgen ray are claimed by some observers in this disease. If it was of any benefit in this patient's case, its effects only showed many years after the exposures and she had many opportunities to die in the interim. I would not like to offer such many-years-in-the-future chances to all the hyperplastic goiters I see.

The effect of Rogers' serum, I think, can also be disregarded.

Prolonged periods of rest and sedatives no doubt aided her over many serious periods of acute hyperactivity, and rest and digitalis no doubt saved her failing heart on many occasions, but it is very doubtful in my mind if specific benefit accrued

from any treatment. She should be regarded as a case in which gradually spontaneous subsidence occurred in a very severe case of Graves' disease. While periods of improvement and sometimes complete subsidence of symptoms commonly occur in the milder types of hyperthyroidism, it is unusual to have one of the serious types continue to show such profound toxic symptoms for so long a period and yet survive.

With our present knowledge of the disease surgery would have been resorted to in this case many years before she reached the condition of advanced intoxication and myocardial damage in which she came to me. While her disability is considerable her survival is rather miraculous. Her case should bring certain facts to our mind, namely, that

(1) Some thyrotoxic cases become quiescent and spontaneous subsidence of toxicity occurs, which cannot be directly attributed to any special treatment.

(2) Mild cases not infrequently do this, the severe typical Graves disease rarely.

(3) Complete disappearance of all signs of enlarged thyroid can occur.

(4) The opposite condition of myxedema may develop in later years.

(5) The residual effects of chronic hyperthyroidism manifest themselves chiefly in damage to the heart muscle, usually considered to be a toxic myocarditis.

(6) Where spontaneous or surgical recovery occurs, the extent of myocardial damage largely determines the patient's future activity.

(7) Any prolonged postponement of surgical measures is likely to result in permanent myocardial damage.



## AN INTRATHORACIC GROWTH SIMULATING ANEURYSM

It is sometimes difficult to differentiate an aneurysm from an intrathoracic growth. This patient I am showing you presented such a problem.

**Case History**—The patient is a traveling salesman, fifty-seven years of age, who applied at the Eye, Ear, Nose, and Throat Hospital a few days ago, complaining of hoarseness of seven weeks' duration.

His family history is not of interest, and he has had no previous illnesses of any consequence. Financial reverses and a large family to support have caused him much worry. He denies lues. He thinks he has noted weakness and slight dyspnea on exertion for six months. His weight is as usual.

**Present Illness**—Seven weeks ago, while drinking orange juice, he seemed to note that "it did not go down the right way," although no coughing occurred. Thirty minutes later he stopped to speak to a friend and found that his voice was very husky. Several weeks later he had attacks of dull pain in his upper left chest radiating through to the scapular region and down the left arm to the elbow. Slight cough developed and a small amount of whitish mucoid sputum he expectorated was reported negative for tuberculosis by the City Laboratory. The throat department sent him to me for examination, with a diagnosis of paresis of his left vocal cord.

You no doubt know that thoracic aneurysm is by far the commonest cause of left vocal paresis, and where such a condition is found you should eliminate aneurysm before considering any other diagnosis. I proceeded with my physical examination with this in mind. The important points of this examination are:

He looks healthy and comfortable. His voice is a loud whisper, he has lost no weight. His pupils are equally contracted and react to light. Head and neck are negative. On inspection of his chest you can readily see that his left clavicle, second left rib, and the upper half of his sternum are lifted with each cardiac impulse. This is very striking and unmistakable, and while not difficult to see, it can best be seen by looking downward over his left shoulder. No abnormally prominent veins are noted on his chest or neck. On palpation, no tracheal tug, no diastolic shock, and no thrill are felt. The pulsation can be felt, however, as well as seen. On percussion note that this dullness in front extends from the right sternal edge 10 cm. to the left and from the left third rib to the clavicle. The heart dullness is slightly downward and outward. Posteriorly dullness is noted between the third and fifth dorsal vertebrae. On auscultation his heart sounds are normal and no bruit is heard. His lungs on auscultation show no alteration of the breath sounds over the dull area and no râles are heard. His blood-pressure is equal in the two arms, 160/110. Vessels sclerotic. Abdomen and ex-

tremities negative Red cells 4,500,000, white cells 10,250, hemoglobin 80 per cent

Small mononuclears, 27 per cent, large mononuclears, 3 per cent, polynuclears, 69 per cent, basophils, 1 per cent Blood Wassermann negative

**Discussion**—I at once made a diagnosis of aneurysm of the aorta, and felt quite sure of seeing a large saccular aneurysm on Roentgen-ray examination At first the fluoroscope seemed to confirm this, as a dense shadow was seen in the upper left



Fig. 202—Plate showing mass in left upper lobe of lung

chest, apparently part of the aortic shadow, but the character of the pulsation in this shadow did not seem satisfactory to the radiologist, and he asked to be allowed to make several plates at different angles and also another fluoroscopic later This further study definitely shows that the mass is not a true expansile tumor, but is a mass in the lung and is receiving its impulse from contact with the normal aorta It is, in all probability, a malignant growth (Fig. 202, made 12/1/23)

Let us analyze his symptoms and signs

*First* His age, fifty-seven, is, of course, that of cancer, but he is not too old for aneurysm

*Second* He thinks he had weakness and slight dyspnea on exertion for six months, then he suddenly developed a left vocal paresis followed by pain in the left chest and shoulder-blade, radiating down the left arm All of which symptoms are very commonly met with in aneurysm and not so frequently in cancer

*Third* A left vocal paresis always carries the suspicion of aneurysm until it is proved otherwise Remember that a right vocal paresis is extremely rare in aneurysm, but suggests pressure from some other type of tumor

*Fourth* This pulsation, which you can all see and feel, is almost pathognomonic of aneurysm when found in conjunction with substernal dulness and left vocal paresis

*Fifth* The absence of a tracheal tug, or thrill, or diastolic shock, or bruit, should not weigh too strongly against aneurysm All of these signs are frequently absent in aneurysm

This man, therefore has a group of symptoms and physical signs which, when carefully considered, are so strongly suggestive of aneurysm that it is only the x-ray examination which tells us the true condition I do not feel upset over having missed the diagnosis The man really should have an aneurysm according to physical signs Another time, under similar circumstances, I might look and think a little longer, but I believe I would diagnose aneurysm and probably be correct

The lesson this case should teach us is that intrathoracic tumors can transmit pulsation to the chest wall when they are in contact with the aorta This pulsation frequently does not differ from that caused by aneurysm The expansile type of pulsation which always distinguishes aneurysm is not often seen in aortic aneurysms unless the sac has eroded the chest wall

*Subsequent Outcome*—While cancer of the lung was the most probable diagnosis, it was thought advisable to try antiluetic treatment and watch results Rather intensive treatment with salvarsan, iodids, and mercury was accordingly carried out for several months No improvement resulted Deep roentgen-ray therapy was then considered and his upper anterior left

chest was exposed several times. Such a severe reaction followed that he refused further exposures. The cough became worse and thick mucoid and occasionally bloody sputum was expectorated. It had the currant jelly appearance frequently seen in lung cancer.

Very little loss of weight was noted and he was still fairly comfortable four months after his vocal paresis had developed. In fact, he might have continued work. But his complete aphonia made it too difficult for him to interview people, and he was



Fig. 203 —Plate made four months after first plate, showing marked increase in size of tumor

given sick leave by his firm. He worried much, although never advised of his true condition. Weakness developed and he began to lose weight. The pain in his left chest radiating down the arm became more severe and required opiates constantly. Another x-ray plate showed a great increase in the size and density of the growth and smaller shadows of metastases in the other parts of the lungs (Fig. 203, made 4/26/24). No doubt of the diagnosis now existed. Shortly after this he became drowsy and rapidly lapsed into a deep stupor with mild de-

linum, stertorous respiration, edema of face and left arm, and died on 5/20/24 Dr John A Lanford made the following autopsy report

Body is that of a well-developed, poorly nourished white male, which has been embalmed and which shows no characteristic marks of injuries on his body

*Peritoneal cavity* is free from inflammation and the relations of the various organs to one another are normal

*Pleural Cavity*—Left pleural cavity is almost entirely replaced by a large neoplastic growth which has encroached upon the wall of the cavity, particularly in its upper anterior and posterior areas Right pleural cavity is somewhat narrow and encroached upon by the tumor mass from the left side crossing the mediastinum

*Pericardial cavity* is negative, but the pericardial sac in its upper area is encroached upon by neoplasm-of the lung

*Lungs*—Right lung is rather doughy in consistency, and here and there can be made out areas of increased density which are relatively sharply defined in the lung tissue and vary in size from a pea to a hen's egg On section it is noted that these neoplastic growths are a gray color and very cellular in appearance

Left lung in its upper and middle portion is taken up by the neoplastic growth which has encroached upon the thoracic wall of the side and involved the structures of the mediastinum, pressing down particularly on the esophagus and pushing the trachea to the right This neoplasm has metastasized to the other portions of the left lung which appear as nodules showing a similar type of structure as the primary neoplasms On sectioning it is found to be whitish gray in appearance, very cellular in character, and has encroached upon the various bronchi which are filled with loose tumor cells forming casts of the bronchi

*Liver* is slightly increased in size and presents here and there a few minute grayish areas which are suggestive of secondary neoplasms

*Spleen* negative.



*Pancreas* negative

*Adrenals* negative

*Kidneys* —Early seat of a chronic interstitial nephritis

*Anatomic Diagnosis* —Carcinoma of the lung, primary in the left lung Secondary carcinoma of the right lung and liver  
Chronic interstitial nephritis

# CLINIC OF DR HAMILTON P JONES

## CHARITY HOSPITAL

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### COMPARATIVE STUDIES OF CEREBROSPINAL FLUIDS, ESPECIALLY IN REFERENCE TO REFRACTIVE INDEX

BEFORE taking up with you at the bedside the several cases of meningitis we now have in the ward, I wish to discuss with you the various laboratory procedures now in use for the purpose of making, through them, differential diagnoses of the usual cerebrospinal conditions, and to impress upon you their relative values and the absolute necessity for strict observance of the technic required and the reasons therefor

Few of these procedures are singly of any diagnostic value whatsoever, any more than an increased blood-pressure or an increased temperature would be, of itself, diagnostic. These various findings are all important, should all be made in each case, and should be correlated so as to get the fullest information from clinical laboratory procedures capable of being afforded

In examining any particular substance it is desirable that we should have that substance in its pure and uncontaminated state. If we are examining cerebrospinal fluid we want to examine cerebrospinal fluid, and not cerebrospinal fluid mixed with blood from an extraneous source or changed in any manner through the medium of a dirty receptacle into which it is received. Spinal puncture while of itself not a particularly painful or dangerous procedure is at times a more or less disturbing and momentous undertaking, particularly in private practice, and it is

N B For valuable assistance in work other than Refractive Index I am indebted to Dr M J Couret, Chief, Dept Path Charity Hosp, New Orleans. Drs A. Gondolf, M P H Bowden, H E Guerriero, P H Jones, and S V McNair, of Charity Hospital. Also to Dr John A Lanford, Pathologist, Touro Infirmary, New Orleans

well to use a proper anesthetic, either general or local, and have the work done as gently and as aseptically as our modern information would indicate

The skull and spinal cavity, within which the brain and spinal cord lie bathed and packed in cerebrospinal fluid, is a non-elastic cavity, therefore the removal of any portion of its contents, the cerebrospinal fluid, for instance, immediately lowers the intracranial and intraspinal pressure, therefore your cerebrospinal pressure reading should be made immediately after the needle has been introduced. There is, of necessity, bound to be a certain wastage of fluid before connections can be made with the spinal manometer, no matter what type it may be, in con-

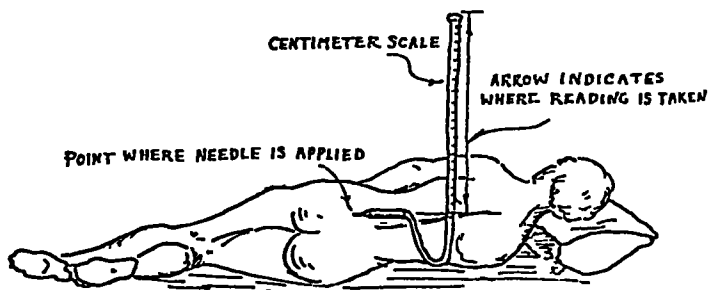


Fig 204—Simple apparatus for estimation of cerebrospinal pressure

sequence of which no manometer reading is ever as high as the cerebrospinal pressure was before the puncture

There are various manometers on the market, but the one which I now show you is entirely inexpensive and is composed of materials which should be always available. As soon as the cerebrospinal fluid starts to flow from the needle a small rubber tube I now show you, having an internal diameter of not over 0.1 inch, is slipped over the shank of a needle (Fig 204). The free end of the tube is now raised and lowered until a point is reached where the cerebrospinal fluid just ceases to run over. The distance is measured perpendicularly from the free end of the tube to the point of entrance of the needle into the spinal canal.

The specific gravity of cerebrospinal fluid averages about 1.006; the specific gravity of mercury is 13.59, therefore roughly,

but sufficiently accurate for all practical purposes, each 136 cm of height of cerebrospinal fluid in your rubber tube is equivalent to 1 mm of mercury pressure. You will see by this that the determination of the cerebrospinal pressure in terms of millimeters of mercury is not difficult, but it is surprising how seldom this determination is made, in consequence of which a very valuable source of information is often lost.

After your spinal pressure has been determined your cerebrospinal fluid is collected in four tubes, which ought to be prepared in the following manner

(1) Wash in tap-water -

(2) Let stand for twenty-four hours in a solution composed of 8 per cent. potassium dichromate and 8 per cent. sulphuric acid in water

(3) Wash in tap-water

(4) Wash in distilled water

(5) Wash in triple distilled water

(6) Dry inverted in a hot-air dryer.

(7) Plug with sterile cotton

(8) Sterilize in hot-air sterilizer at 170° C for one and a half hours. It is preferable, of course, to use new tubes if available

These tubes are numbered 1, 2, 3, and 4 respectively. In Tube No 1 a small amount of spinal fluid is collected unless it is bloody. Should it be bloody, a larger amount is collected. In Tube No 2 a small amount of fluid is collected unless it is bloody, in which event a procedure as in Tube No 1 is repeated. In Tube No 3 the largest amount is collected, say 4 or 5 c c, and in Tube No 4 not less than 1 c c of fluid is collected.

The object of this is to obtain blood-free fluid in absolutely clean tubes, especially in Tubes 3 and 4. Tube No 3 is used for cell count, globulin, Wassermann, and refractive index reading, while Tube No 4 is used for colloidal gold reaction. It is very annoying to find that a cerebrospinal fluid has to be discarded because of the lack of observation of these simple but absolutely essential steps. It is manifestly impossible to make a proper cell count when there is a lot of blood present. It is

often the case that you have a positive blood Wassermann with a negative cerebrospinal Wassermann, but how are you going to tell where the reacting substance comes from if you have a lot of blood contaminating the cerebrospinal fluid, or you have some fatty substance in a dirty tube that gives you a misleading Wassermann reaction?

Up to this time the principal complete routine examinations of cerebrospinal fluid have consisted in a request for the clinical laboratory to make cell count, globulin determination, sugar determination, Wassermann reaction, and colloidal gold reaction. The cell count is of extreme importance, especially in the inflammatory conditions, and oftentimes a very valuable suggestion is made by the differential count, but there are many instances in which you have very grave changes in the cerebrospinal system in which the cell count gives no indication whatever as to the true nature of the trouble, oftentimes being negative where you would expect it to be positive. The same may be said of the globulin reaction. The determination of the amount of globulin is of interest, and in the differential diagnosis may throw light one way or another, but, of itself, cannot be considered of definite diagnostic value. Generally speaking, the amount of sugar found in syphilitic meningitis, tuberculous meningitis, anteriopoliomyelitis, and especially in encephalitic lethargica is normal or above, although there are exceptions to this.

The Wassermann reaction may or may not be positive, and while, if positive, it is of distinct diagnostic value, if negative the reading cannot be accepted as an expression of the truth.

The colloidal gold reaction is of very great diagnostic importance and should be given the greatest consideration in coming to a conclusion as to the diagnosis of any particular case. However you must understand that generally a man is well before he gets sick and that after being sick he may get well, and that the cerebrospinal fluid is subject to change during the course of the disease which would give you findings at one time entirely different from those of another, especially in cere-

brospinal lues, and some of the acute meningitides that have been successfully treated

I have for many years felt that the information afforded by the various tests just mentioned has not presented all the evidence that we would like to have in reference to the actual state of the cerebrospinal system of the person under observation, particularly in those cases where the character of the spinal fluid, as to clearness or cloudiness, the microscopic examination of the smear, and the result of the culture do not throw any illuminating information on the situation

One of the unfortunate things about the practice of medicine is that the field is so large that it is practically impossible for a man, even though he may know it all to think of it all at the time he is handling any particular case. There are many general laboratory procedures in every-day use in general laboratories all over the world that would be, if applied to the study of body secretions etc. of the utmost importance. A number of years ago, when I was State Analyst and Food Commissioner for the State of Louisiana, I became familiar with the use and application of an instrument called the refractometer, which is based upon the physical principle that each substance has a specific power of refracting or bending a ray of light. For instance, diamond merchants have a special type of refractometer devised so as to measure the refractive power of various gems submitted to them so that they can absolutely determine the quality and kind of stone that they have under observation. The instrument is extensively used in dairies for the purpose of determining the purity of butter fat, and by dealers in olive oil and linseed oil and various commodities for determining the purity of the products submitted to them for purchase etc. The refractive indices of various commodities are so specific for the substance under consideration and the use of the instrument is so simple that it is of universal use.

It had occurred to me that studies of the refractive indices of such fluids of the human body, in health and disease, as were available, would in all probability, show characteristic refractive indices concomitant with certain diseases to which the human

body might be subject, so that during the past summer I have been making observations of the refractive index in consonance with the routine clinical laboratory observations on cerebrospinal fluids and blood-plasma from a wide variety of cases

As we are dealing this morning entirely with the cerebrospinal fluid I will set aside for another time my conclusions as to the value of this instrument in studies of the blood-plasma. There are a great many different types of refractometers on the market, but I have selected the Spencer Abbe refractometer because it only requires a small amount of fluid, not over  $\frac{1}{2}$  c c, and has a convenient temperature controlling device by which observations can be made at any desired temperature. It is accurate to the fourth decimal place, which seems to be sufficient for the purpose at hand.

You must understand that when I started this work it was an entirely new thing to me and I had no experience of others to go by. I therefore arbitrarily determined to make all my readings by daylight and at a temperature of  $20^{\circ}$  C. I selected this temperature because, while a little low for average work in New Orleans, it would probably be an acceptable temperature for the temperate zone at large. One of the objections to having your temperature low is the accumulation on the cool surface of condensation moisture from the atmosphere, but this is very easily controlled by having a dry cloth to constantly wipe off the accumulated moisture.

After I had been working for about a month on this matter I secured copies of all the articles that had been published, so far as is known, upon this subject. The principal work was done by Babes and Babes in 1913 and 1914, Palmegiani in 1914, and Molnar in 1923, whose work consisted in the study of the refractive indices in various diseases, without reference to any of the concomitant conditions found in the cerebrospinal fluid, except Babes and Babes, in their article of January, 1914, who made a critical study of the relationship of the refractive index to the chemical constituents of the examined cerebrospinal fluid, which tended to prove that the increase in the refractive index was rather dependent upon the amount of organic sub-

stances present, particularly albumin, than the inorganic substances which did not seem to vary much between 7 and 8 grams per 1000 c c.

My own observations in reference to this matter have not led me to any satisfactory conclusions. I have prepared a tabulation, which I now show you, of a number of spinal fluids critically studied from a diagnostic standpoint, and, as you will see, carefully worked out from the clinical laboratory side. These comparisons, so far as I know, are the first that have been made of this nature in reference to the refractive index.

*Cerebrospinal Lues*—You will note that there are 16 cases of undoubted cerebrospinal lues tabulated in the first chart, with an average refractive index of 1.335268, an average cell count of 209, an average globulin content of 1+, average sugar content of 63.3, positive Wassermanns, 13.2 per cent, cerebrospinal pressure normal in most cases, the fluid is clear, smear and culture negative, the colloidal gold, where made, confirmatory, while the blood Wassermann was positive in only one instance.

Cases 21 and 39 in the same chart, judging either by the high refractive index or high cell count, were undoubtedly cases of cerebrospinal lues, while Case 72, judging by the refractive index, shows that, as yet, there has been no involvement of the central nervous system.

*General Infectious Lues*—Cases 11, 25, 53, and 55 (Chart 2) are cases of general infectious lues, so-called secondary stage. It will be noted in these cases (11, 25, 53) that the refractive index is normal, whereas in Case 55 the refractive index is above that of the average for cerebrospinal lues, all the other factors being negative. I am, therefore, forced to conclude that the high refractive index in Case 55 is an evidence of an early involvement of the cerebrospinal system of this case by the luetic infection. This is particularly interesting and may, I hope, be a means, after further study and confirmation of this work, of determining early involvement of the cerebrospinal system in syphilis, the effects of treatment, and, possibly, a satisfactory means of determining a cure in this condition.



CHART 1

COMPARATIVE STUDIES OF CEREBROSPINAL FLUIDS, ESPECIALLY IN REFERENCE TO REFRACTIVE INDEX

Series number	Age	Diagnosis	Refractive index at 20° (°)	Cell count	Globulin	Sugar	Wassermann	Blood Wassermann	Remarks
1	11	Genl paresis	1.3177	6	1+		4+		Colloidal gold 2234
4	11	C. S. luc.	1.3351	1			Neg.		421000
5	20	C. S. luc.	1.3313	10	1+	62	Neg.		Character Clear
6	20	C. S. luc.	1.3317	40	1+		Neg.		Character Clear
14	34	C. S. luc.	1.3317	161	2+		Neg.		
17	18	C. S. luc.	1.3352	41	1+		Neg.		
18*	15	C. S. luc.	1.3356	2	1+		Neg.		
19*	45	C. S. luc.	1.3357	6	1+	45	Neg.		
20	24	C. S. luc.	1.3355	1			Neg.		
24	24	C. S. luc.	1.3350	2			Neg.		
26	40	C. S. luc.	1.3319	1		76	Neg.		
30	40	C. S. luc.	1.3318	2			Neg.		
36	37	C. S. luc.	1.3356	12	2+	98	4+		Colloidal gold 5554
63*	37	C. S. luc.	1.3351	11		55	Neg.		432000
64	35	C. S. luc.	1.3350	1			Neg.		Colloidal gold 1243
66	35	C. S. luc.	1.3355	58	2+		Neg.		310000
			1.335268	20 9	1+	63 3	13 3%		
21*	42	Ch enterphalitis	1.3357	1			Neg.		
19*	7	Parvovirus	1.3319	7	2+		Neg.		
		Rickets pul T. B. luc.		1	1+	68	Neg.	4+	Colloidal gold 0001
72	5	Rickets Ren luc.	1.3153	3					333220
			1.3140	1					

\* Very probably cases of cerebrospinal luc.

N B Clear cut evidence of pathology of the cerebrospinal system present in each of these cases

# STUDIES OF CEREBROSPINAL FLUIDS, ESPECIALLY IN REFERENCE TO REFRACTIVE INDEX

Series number	Age	Diagnosis	Refractive index at 20° C	Cell count	Globulin	Sugar	Wasser mann	Pressure	Blood Wasser mann	Blood refractive index at 20° C	Remarks	Remarks
11	36	Gen inf lues	1.1112	1			Neg			1.3511		Charmeter Clear
25	46	Gen inf lues	1.1111	2			Neg	7 mm	1+	1.1408		Charmeter Clear
51	21	Gen inf lues	1.3311	2		62	Neg	6 mm	1+	1.3502		
55	19	Gen inf lues	1.3353	1		71	Neg		1+			
57		Gen inf lues	1.3311+	— 2	—	66.5	Neg	7 mm	(1) 1+ (2) —	1.15136		Charmeter Clear

### CIART 3

[illegible]

**CHIARI &**

[illegible]

*Tuberculous Meningitis*—Cases 9, 13, and 23 (Chart 3) are cases of tuberculous meningitis, all of which died and went to postmortem. It will be noted that the refractive index is constantly high, although not averaging quite so high as is found in cerebrospinal lues. Case 23 is of particular interest because the first refractive index made on the 18th of the month was 1.3344 (normal), the high cell count, 4+ globulin, normal sugar content, increased pressure, hazy fluid, but no acid fast bacilli found. On the 22d the refractive index has gone up to 1.33533, and the sugar has gone down to 37 mm per 100 c.c. This refractive index was maintained until the patient's death. It is of interest to note in this case that with the diminishing globulin and diminishing sugar content the refractive index should rise, showing the necessity of further critical study of the cerebrospinal fluid so as to give us a clearer understanding as to the nature of changes in disease.

*Encephalitis Lethargica*—Cases 7, 15, and 37 (Chart 4) are cases of encephalitis lethargica. It will be noted that the refractive index in these cases averages 1.3343, which is within normal bounds. There is an increase in cell count, an increase in globulin, and a high sugar content, but not so high as that found in general infectious lues. The refractive index, I believe, will be of extreme importance in making differential diagnoses in reference to this condition.

*Meningococcic Meningitis*—There is only 1 case recorded, Case 3 (Chart 5), with high refractive index, 1.33542, high cell count, increased globulin. Unfortunately, no sugar determination was made in this case.

*Influenzal Meningitis*—Case 68 (Chart 6). High refractive index, going up from 1.3356 to 1.3364, as did the refractive index in Cases 23 and 37 (Charts 3 and 4), very high cell count and globulin content, with low sugar content, averaging 29.5.

*Paralysis Agitans*—Cases 8, 27, 35 (Chart 7). The refractive index averaging 1.3343, which is normal, other laboratory findings negative.

*Hysteria*—Case 42 (Chart 8). Normal refractive index 1.3340, all other findings normal except high sugar, which is 80 mm per 100 c.c.

# CHART 5

## COMPARATIVE STUDIES OF CEREBROSPINAL FLUIDS, ESPECIALLY IN REFERENCE TO REFRACTIVE INDEX

Series number	Age	Diagnosis	Refractive index at 20° C	Cell count	Globulin	Sugar	Wassermann	Blood Wassermann	Blood serum refractive index at 20° C	Remarks	Remarks
3	4	Meningococcal meningitis	1.33512	1410	3+		Neg			Culture — Pressure 14 mm Character	Cloudy, Smear Pus G N fine

# CHART 6

68	16 mos	Influenzal meningitis	1.3356	7500	1+	32	Neg			Culture G N Bacilli, Character Pressure 14 mm	Cloudy, Smear Pus G N fine
64		Influenzal meningitis	1.3362	2100	1+	27	Neg				Total W B C on admission 8000, four days later, 25,600
68		Influenzal meningitis	1.3364	2175	1+		Neg				
			1.33607	3925	4+	29.5					

# CHART 7

8	30	Paralysis agitans	1.3347	3			Neg				
27	46	Paralysis agitans	1.3343	—1			Neg				
15	55	Paralysis agitans	1.3341	—	—		Neg				
			1.3313+	+1							

# CHART 8

42 <sup>B</sup>	38	Hysteria	1.3310	1		80	Neg			Culture —, Smear —, Character	Clear, Pressure 10 mm
42 <sup>B</sup>	38	Hysteria	1.3310	—	—	80	Neg				
			1.3340	1							

*Cerebral Hemorrhage*—Cases 2 and 45 (Chart 9) Refractive index within normal bounds, with other findings normal

*Alcoholic Psychosis*—Cases 10 and 90 (Chart 10) Case 90 gave some clinical evidence of cerebrospinal lues

*Pellagra*—Cases 61 and 65 (Chart 11) Give rather high refractive index, with other findings negative, except sugar, which is slightly below normal

*Traumatic Injuries to the Head*—Cases 34, 47, and 52 (Chart 12) Give an average low refractive index, 1.3339 In none of these cases was the cerebrospinal fluid bloody, but if it should be, a higher refractive index should be expected

*Miscellaneous Cases*—Cases 12, 16, 40, and 54 (Chart 13) These all give refractive index within normal limits, with other findings negative

*Infantile Convulsions*—Case 38 (Chart 14) This child had whooping-cough fourteen days, entered the ward for convulsions, was found to have also bilateral bronchopneumonia, and died within three hours of admission The refractive index was 1.3385, the highest index that I have as yet read on any cerebrospinal fluid, the other laboratory findings were negative This finding would naturally lead one to suppose that very serious changes must take place in all cases of convulsions, particularly of infancy, and that it is not safe to assume that they are due to irritation or purely reflex action, that, as a matter of fact, all cases of convulsions are associated with cerebrospinal changes sufficient to markedly influence the character of the cerebrospinal fluid

In conclusion I will say that it appears to me that the determination of the refractive index of the cerebrospinal fluid in the diseases so far examined develops the fact that it appears to be the most constant factor of all of the factors used from a clinical laboratory standpoint, so far developed That of itself, it is naturally not diagnostic, it is only suggestive This is only a preliminary report, and I sincerely hope that further investigations will be made along these lines so as to place the determination of the refractive index in its proper position as one more aid toward making a diagnosis

# CHART 9

## COMPARATIVE STUDIES OF CEREBROSPINAL FLUIDS, ESPECIALLY IN REFERENCE TO REFRACTIVE INDEX

Series number	Age	Diagnosis	Refractive index at 20° C	Cell count	Globulin	Sugar	Wassermann	Blood Wassermann	Blood serum refractive index at 20° C	Remarks	Remarks
2	19	Cerebral hemorrhage	1.3311	—1							
45		Int nephritis	1.3346	3			Neg				
		Rt hemiplegia	1.3313	2	—		Neg				

# CHART 10

90	31	Alcoholic psychosis	1.3350	—1	+1		Neg			Colloidal gold 1:111	
10		Edema of brain	1.3311	—1	—		Neg			100000	
			1.3365	—1							

# CHART 11

61	40	Pellagra	1.3350	—1		10	Neg		1.3150	Culture —	Blood sugar 98
65		Pellagra	1.3350	—1	—	18	Neg		1.3512		
			1.3350	—1		11	—		1.3181		

# CHART 12

34	20	Lac wound of head	1.3311	1			Neg			Smear neg	S R, many R B C present
47	5 mos	Birth injury, head	1.3315	3			Neg				
52	6	Skull fracture	1.3312	—	—		Neg				
			1.3339 ±	3½							

# CHART 13

## COMPARATIVE STUDIES OF CEREBROSPINAL FLUIDS, ESPECIALLY IN REFERENCE TO REFRACTIVE INDEX

Series number	Age	Diagnosis	Refractive Index at 20° C	Cell count	Globulin	Sugar	Wassermann	Blood Wassermann	Blood serum refractive index at 20° C	Remarks	Remarks
12	2½	Tetanus ninth day	1 3345	—1			Neg				
34	1½	Chronic gastritis	1 3342	5			Neg				
16	1½	Hemolytic strep Septicemia	1 3349	1		14	Neg		1 3486	Smeat neg	Smeat —, Culture — Character, Clear Pressure 8 mm
40	33	Uterine fibroid	1 3342	—	—		Neg				Item "Dare" 33% Blood Cal 11 mm
			1 33446								

# CHART 14

Series number	Age	Diagnosis	Refractive Index at 20° C	Cell count	Globulin	Sugar	Wassermann	Blood Wassermann	Blood serum refractive index at 20° C	Remarks	Remarks
38	6 mo	Convulsions	1 3385	—2			Neg				

\* Whooping, cough fourteen days bronchopneumonia, one week, entered with convulsions and died in three hours No postmortem permitted

**SUPPLEMENTARY CHART**  
**COMPARATIVE STUDIES OF CEREBROSPINAL FLUIDS, ESPECIALLY IN REFERENCE TO REFRACTIVE INDEX**

Series number	Age	Diagnosis	Refractive index at 20° C	Cell count	Globulin	Wassermann	Colloidal gold	Remarks
A	(Ages from 28 to 45)	S lues	1 3358	0-1	1+	3+	4432211000	Meningitic type Diplopia meningitic type basilar Undoubtedly tabes  Organic condition of cord about eighth to ninth dorsal, evidence of compression
B		C lues	1 3350	1-2	1+	3+	44322311000	
C		S lues	1 3358	13-14	1+	Neg	00001110000	
D		S lues	1 3352	4-5	3+	3+	44432211000	
E		S lues	1 3355	0-1	1+	Neg	00001110000	
F		S lues	1 3356	14-15	1+	Neg	11110000000	
G		S lues	1 3353	6-7	2+	3+	13432110000	
H		C lues	1 3350	5-6	Neg	Neg	00122100000	
I		S lues	1 3350	2-3	2+	Neg	4333210000	
J		S lues	1 3353	3-6	1+	Neg	00012210000	
K		S lues	1 3352	23-24	3+	4+	00123320000	
L		C lues	1 3355	23-26	2+	3+	00123210000	
			1 33535		1 63			
M		Normal	1 3346	0-1	Neg	Neg.	00001110000	Tumor of brain
N		Normal	1 3346	3-4	Neg	Neg		
O		Normal	1 3346	2-3	Neg	Neg	00011110000	
P		Normal	1 3347	3-4	1+	Neg		
Q		Normal	1 3317	2-3	Neg	Neg		
R		Normal	1 3346	2-3	1+	Neg	00012200000	
			1 33463		(4) 1+ (2) 1+			



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## CLINIC OF DR SAM HOBSON

### CHARITY HOSPITAL

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#### ARTERIOVENOUS ANEURYSM

THE case presented before you today is that of an arterio-venous fistula. Its presentation is believed opportune for the reason that it so well exemplifies the cardiovascular and systemic effects of such a pathologic complex.

H F, aged fifty-eight years (Figs 205 and 206), admitted to hospital because of dyspnea and edema of lower extremities.

*History*—At twenty-two years of age was shot in neck just below right mandible, the bullet entering from behind and coming out through mouth, piercing the upper lip. He experienced no trouble from this until about six or seven days later, when he noticed a "buzzing sensation" in the neck. At that time a small mass (about the size of a pecan nut) was noted just below the middle of the lower border of the mandible on the right side. Neither the mass nor the "buzzing sensation" in neck disturbed him until three years ago, when, due to a sudden overexertion (in a fit of anger), he felt a "pull" in his neck, shortly afterward noticing that the mass was the size of a hen's egg. The mass grew slowly from that time on, and the "buzzing" was more marked, but he had no discomfort except slight pain and some shortness of breath when coughing. In the early part of 1925, following pneumonia, the mass began to increase rapidly in size and the "buzzing" became more pronounced, he then experienced marked dyspnea and edema of both arms and legs. He denies ever having had venereal disease.

*Physical Examination*—A colored male propped up in bed, and showing considerable difficulty in breathing. The right eye protrudes. There is a mass on the right side of the neck about the size of an orange. On palpation a marked thrill is noted over this mass, which thrill is continuous throughout systole and diastole. On auscultation a loud murmur is heard throughout systole and diastole over the above noted mass, with a systolic murmur over all of the clinical valvular areas, loudest however over the mitral area. In the region of the left sternoclavicular articulation a tortuous mass about the size of a medium grapefruit is noted. This is apparently a mass of enlarged injected, tortuous veins. The apex beat is noted in the sixth interspace 15 cm from the midsternal line. The right border of the heart extends in the fourth interspace to a point 5 cm beyond the midsternal line. The left border extends in the fifth interspace 17 cm beyond the midsternal line.

The blood-pressure, repeatedly taken, averages 210 systolic and 90 diastolic. Upon compression of the mass at the site of the fistula an increase in both the systolic and diastolic pressures to an average of 218 for the systolic and 98 for the diastolic is repeatedly noted. Such compression causes the pulse rate to drop 16 beats per minute (Branham's sign).

The clinical pathologic findings are as follows:

Urine reveals 5 per cent albumin with a few hyaline casts.

Phenolsulphonephthalein excretion 35 per cent in two hours.



Fig. 205—Arteriovenous aneurysm. Lateral view, showing size of sac and tortuous, distended veins.

Blood Wassermann negative.

Blood-picture: Total red cell count, 4,500,000, total white cell count, 9250, hemoglobin, 75 per cent. Small mononuclears, 21, large mononuclears, 5, eosinophils, 1, neutrophils, 73.

Basal metabolic rate not obtainable due to patient's condition.

Electrocardiograms, secured through the kindness of Professor George R. Herrmann (Fig. 207), show a definite left ventricular preponderance. There is an increased P-R interval (0.22-0.24 sec.), indicating delayed A-V conduction, with negative and diphasic T waves. (Both of these latter are

probable results of digitalization ) There are occasional R ventricular extrasystoles

The x-ray examination (Fig 208), conducted by Professor Amedee Granger, gives the following information "The screen study shows a very large pulsating mass in the right supraclavicular and cervical regions The plates, postero-anterior and oblique views, show marked increase in the transverse and longitudinal diameters of the heart, and marked increase in the diameters of the aorta The contour of the ascending portion of the arch of the aorta is very indefinite, the apex region of the right lung is obscured by the shadow of the pulsating mass seen under the screen We are



Fig 206 —Arteriovenous aneurysm Front view, showing percussion outline of right and left cardiac borders

forced to conclude that this patient has an enlarged and dilated heart, that the aorta is enlarged, and that the pulsating mass is very probably connected to the right innominate "

Here evidently is a case of arteriovenous fistula exhibiting cardiovascular disorders which, at the present time, cause practically total disability A detailed consideration of these various

disorders and a full discussion of the many physiologic and pathologic features of the case are far beyond the time allotted for this conference. We must, therefore, consider in a synoptic manner the most salient features thereof

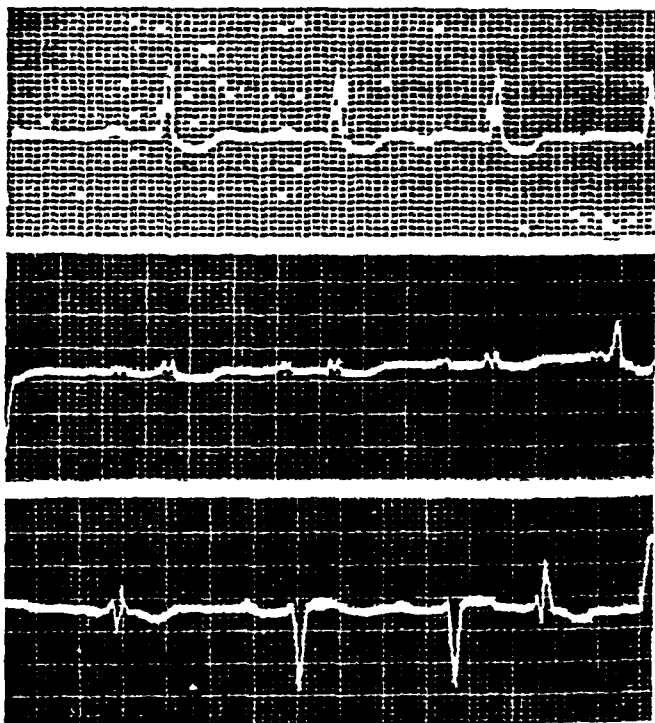


Fig 207—Arteriovenous aneurysm. Electrocardiograms, Leads I, II, and III, from above downward. From case of carotid jugular arteriovenous aneurysm showing definite left ventricular preponderance, an increased P-R interval (0.22–0.24 sec), indicating prolonged A-V conduction and negative diphasic T waves, both of which findings are probably the results of digitalization. Occasionally ventricular extrasystoles. (George R. Herrmann.)

The important systemic or cardiovascular disorders exhibited by such patients either when they are such as to be more or less tolerated, or either when they cause total disability, are

- 1 Enlargement of the heart
- 2 Cardiac murmurs, especially apical systolic murmurs

### 3 Acceleration of the heart rate

4 Slowing of pulse and rise of blood-pressure upon temporary suppression of the fistula (Branham's bradycardiac phenomenon)

Of the less important disorders, helpful however in diagnosis and in full understanding of the physiologic and pathologic aspects of the complex, must be mentioned the Lewis and Drury capillary pulse sign, the Hill and Rowland systolic-pressure-discrepancy between arm and leg, the discrepancy between systolic and diastolic blood-pressure, with high systolic and low



Fig 208—Arteriovenous aneurysm (carotid jugular) Roentgenogram of chest, postero-anterior and lateral views, showing size of heart and aorta Transverse diameter of heart 21.2 cm, longitudinal diameter 19.5 cm

diastolic readings, and the increased respiratory rate with diminished vital capacity

The enlargement of the heart so well established at present as a fact in these cases has given rise to considerable discussion as to its exact nature and cause. In some cases it appears that the enlargement is associated with dilatation alone, in others with hypertrophy, in some there appears an enlargement affecting the heart as a whole, with preponderant left ventricular increase, in others, the increase seems to be especially right sided. Possibly the safest conclusion to be reached as to the nature of the enlargement is that it is a primary dilatation with secondary hypertrophy.

The cause of this dilatation and hypertrophy is readily explainable if one accepts the view that the increased volume of arterial blood injected through the fistula into the veins causes a rise in the venous pressure, this is simply a physiologic compensation theory—primary dilatation and secondary hypertrophy caused by increased work thrown upon the heart in its efforts at moving the increased amount of blood from venous to arterial systems. Lately considerable experimental and clinical evidences have accumulated to disprove this simple physiologic compensatory theory. These studies seem to show that no notable changes in the normal pressure of the venous circulation occurs and that the input and output of the heart is either normal or just below normal, consequently, there can be no increased work of the heart. Attempts at explaining the cause of the dilatation and eventual cardiac hypertrophy is then resorted to in the theory of deficient nutrition of cardiac muscle the result of the fall in arterial pressure. This theory seems impressive, especially in view of the fact that its explanation is essentially upon the lines offered for the explanation of various phases of the symptom-complex seen in aortic regurgitation. It is noteworthy that there is a close analogy between the signs of circulatory disturbances seen in arteriovenous fistula and of those seen in aortic insufficiency.

The cardiac murmurs noted in these cases may be transmitted directly to the heart and pulmonary tract by means of the blood-stream or may be dependent upon an intrinsic cardiac defect, *e g*, the so-called Stewart murmur. The transmitted murmur, of which the Mahans duplicated murmur is a type, disappears upon suppression of the circulation in the injured artery, while the central types are not so silenced. It is especially notable that the Stewart murmur has so far been observed only in arteriovenous fistulae. In most cases it seems to be due to a dilatation of the right heart.

Acceleration of the heart rate is possibly best explained by loss of vagal tone—the inhibiting complex not responding. This is most probably the result of a fall in the average arterial blood-pressure.

The bradycardiac phenomenon of Branham is interesting, especially in so far as it is peculiar to arteriovenous fistulæ only. This remarkable slowing of the pulse upon suppression of the fistula is accompanied by a rise in both the systolic and diastolic pressures, together with a contraction of the cardiac mass along with changes in its shape and position as viewed under the fluoroscopic screen. The surgeon places great stress upon this phenomenon in an attempt at gaging the recovery capacity of the cardiac apparatus after suppression of the fistula (Matas). Recent interesting cardiographic studies (Heninger) show that the slowing in heart rate is at the expense of diastole with no disturbances in rhythm, and with normal complexes. Most interesting is a recent observation of the undisturbed pulse pressure either with the fistula open or closed. No plausible explanation seems possible for this latter





## CLINIC OF DR ELIZABETH BASS

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### TUBERCULOSIS OF THE TONGUE

FINDING very little in the text-books on this subject and less than 300 cases reported in the literature, encourages me to place on record 2 additional cases that are apparently primary

In proportion to the vast number of persons suffering from tuberculosis and considering the large number of tubercle bacilli that must come in contact with the tongue, especially in the case of pulmonary or laryngeal tuberculosis, the number of cases published would seem very small

Inquiry has been made of several leading specialists who see many patients in private practice, clinic service, and institution work in our large medical centers, and no other cases found This coincides with the statements made by the various writers as to the infrequency of the disease in other metropolitan cities

Historical Note — Morgagni<sup>1</sup> in 1761 described what he termed "tubercles on the tongue," but did not clearly define his meaning of the word tubercle In 1804 Portal<sup>2</sup> was credited with the report of the first authentic case of tuberculosis of the tongue Portal was followed by Louis,<sup>4</sup> 1825, Renaud, 1831, Fleming,<sup>4</sup> 1850, Gildmeister,<sup>4</sup> 1852, Paget,<sup>4</sup> 1858, Toland,<sup>3</sup> 1859, Wagner,<sup>4</sup> 1862, and Virchow, 1864,<sup>4</sup> who was the first to report a case from autopsy All of these cases were secondary to tuberculosis elsewhere in the body, chiefly in the lungs

Scarcely 30 cases of primary tuberculosis have been recorded The first case was by Enteneur<sup>4</sup> in 1872 The patient was operated on for carcinoma in mistaken diagnosis In 1876 Clarke<sup>5</sup> reported a case which was operated on for tuberculosis of the tongue The patient died later of some other cause and com-

plete autopsy revealed no other tuberculous lesion Schlieferowitsch<sup>6</sup> in 1887 reported a similar case which showed no other evidence of tubercular infection

Necropsy reports on tuberculous subjects show a very low percentage of lingual tuberculosis Adam,<sup>7</sup> in 417 necropsies, found none von Ruck<sup>8</sup> in 1912 was able to tabulate a grand total of 25 cases from 3935 autopsies reported by different men

Only 1 case of tuberculosis of the tongue could be found among 12,369 patients in German sanatoria There were 19 cases observed in Winyah Sanatorium over a period of twenty-three years, in a total of 5000 patients Morrow and Miller<sup>7</sup> report a much higher percentage They observed 14 cases among 1444 patients within four years in the tuberculosis department of the University of California service at the San Francisco Hospital

**Etiology.**—Tuberculosis of the tongue, whether primary or secondary, is caused by the implantation and proliferation of the tubercle bacilli in the tissue of the tongue The infecting organisms may gain entrance in several different ways (*a*) By direct inoculation from outside the body, (*b*) by inoculation from the sputum, as in pulmonary or laryngeal tuberculosis, (*c*) by spreading from adjacent tissue, as in lupus vulgaris of the face, cheeks, or lips, and (*d*) by inoculation through the blood- or lymph-stream, as in miliary tuberculosis

The relative infrequency of tuberculosis of the tongue is thought to be due to the natural immunity which the buccal cavity seems to possess against various forms of virulent organisms This may be partly accounted for by the general resistance of striated muscle to bacterial invasion, to the thickened mucous membrane, to the almost constant motion of the tongue, together with the cleansing effect of the secretions, and, perhaps, to other unknown factors

**Pathology.**—The pathologic manifestations may be in one of several forms

1 The tuberculoma, which usually appears as a single nodule and may be either superficial or deep in the muscular structure

of the tongue It is commonly mistaken for a neoplasm or gumma, and is often the antecedent of an ulcer One of my cases belongs in this group

2 The cold abscess type is rare, only 3 typical cases are reported

3 The papilloma or warty type is infrequent Scott in 1912 collected in the literature 6 cases

4 The lupus form occurs when there is direct extension from a similar lesion of the face, cheeks, or lips One of the most classical cases in the literature is the one described by Mr Henry T Butlin in his treatise on Diseases of the Tongue, published in 1885

5 The fissure type is fairly common and is usually very painful

6 The ulcer is the most frequently encountered, and may be situated at tip, lateral margins, dorsum, and occasionally at the base of the tongue

Finney and Finney<sup>4</sup> describe a tuberculous ulcer as "usually rather shallow, with indefinite irregular, almost serpentine edges, which, as a rule, are not indurated The base is usually covered with a grayish-white material penetrated in places by tufts of rather pale unhealthy looking granulation tissue The ulcers may be single or multiple and show a marked tendency to heal and then break down again, either wholly or in part At times, on close inspection, small tubercles may be seen just beyond the edges of the ulcer These tend to coalesce, break down, and thus advance the ulcer "

Mr Butlin<sup>9</sup> says, "The general anatomy of tuberculous ulcers of the tongue does not differ in any important respect from the general anatomy of tuberculous ulcers of other parts of the body, except that there is not perhaps, so strong a tendency to caseation as in tuberculous disease of such parts as the lungs or glands Nor does the minute anatomy of the disease differ materially from that of other parts There is the same infiltration of the tissues with small round cells, the same occurrence of the so-called giant-cells, the same arrangement of epitheloid cells, and the same reticulum "

**Incidence.**—Tuberculosis is far more frequent in men than in women, which, as Mr Butlin says, "in this respect resembles cancerous and syphilitic ulcers" Some authors give instances of 4 to 1, others of 5 to 1 The majority of cases are in adults between the ages of thirty and fifty years, however, several cases are reported seen much earlier (Fantozzi<sup>13</sup> collected 4 cases under ten years of age), while there are others in which the lesions appeared much later in life (one of Handfield-Jones<sup>10</sup> patients was eighty years old) One writer mentions the disease as another of the "afflictions of middle life"

Finney and Finney call attention to a very interesting observation in that no case has been discovered in the negro, despite the great prevalence of tuberculosis in this race

**Symptoms.**—The symptoms of which the patient complains vary with the type of lesion represented This is true of tuberculosis located elsewhere in the body There are generally no symptoms until ulceration and secondary infection occur The early symptoms are slight pain and burning in the ulcerated area Late in the course of the disease pain, salivation, and limited motility of the tongue may be so marked as to interfere with eating and speaking The regional glands are involved in some cases, occurring more frequently in the ulcerative type

**Diagnosis.**—The diagnosis of tuberculosis of the tongue must be differentiated from carcinoma, syphilis, traumatic and infectious ulcers, and benign tumors The diagnosis is made principally on the actual appearance and clinical characteristics of the lesion itself, the proving of an active tuberculous lesion elsewhere, the microscopic examination of material removed, both for organisms and tubercle formation, serologic tests, and the inoculation of susceptible animals

A carcinoma is usually more indurated, is almost always solitary, and can be diagnosed by pathologic examination It tends to occur in the same sex, about the same location, and rarely under thirty years of age Tuberculosis occurs in much younger persons

John B Murphy,<sup>11</sup> writing on this subject, says "In tuberculous process repair commonly goes on in one area while destruc-

tion of tissue is taking place in another. If you find in one place an ulcer that is healing and in another one an area that is breaking down, you can conclude at once that it is not carcinoma. But note that if the malignant mass has been cut into, it may heal in one place and break down in another."

A striking feature of the tuberculous ulcer of the tongue is the indolency of the ulceration and it does not readily respond to local treatment.

In the traumatic ulcers prompt healing occurs as soon as the source of trauma is removed. The infectious ulcers are seldom limited to the tongue and they generally respond readily to local treatment.

The benign tumors are of short duration, give no symptoms, and may occur at any age.

**Prognosis**—The majority of surgeons agree that in primary tuberculosis of the tongue the prognosis is good when the entire lesion is removed by wide excision. Secondary tuberculosis of the tongue usually comes late in the course of the disease elsewhere in the body, and most all of the cases end fatally. In several instances relief of pain and comparative comfort has been given the patient by the surgical removal of the ulcer.

The opinion expressed by some of the more recent writers is that except in a few instances the results seem to be the same—temporary improvement with healing and relief, and a subsequent, usually prompt, recurrence of the trouble in spite of continued treatment.

**Treatment**—Many different forms of treatment have been advocated, such as local application of iodoform powder, lactic acid, silver nitrate, and many other therapeutic agents. General treatment with injections of salvarsan and tuberculin have been tried but are not recommended by the more recent writers. Local cauterization, excision with or without the regional glands, and total extirpation have been done. Some writers seem to think the use of radium, violet ray, and Roentgen ray give temporary relief in selected cases.

Morrow and Miller<sup>7</sup> report in one of their advanced pulmonary cases that the tongue of the patient remained well for

monary tuberculosis There were several minute ulcers which soon coalesced Microscopic examination of the sections showed typical tuberculosis There were tubercle bacilli in the giant-cells and the submaxillary glands were caseous

(6) von Eberts,<sup>17</sup> 1808, reported a case of tuberculoma of the tongue in a woman aged twenty-five years The patient complained of a sore tongue and swelling of the glands of the neck There was an intralingual tumor beginning as a deep-seated induration immediately to the right of the median line of the tongue 1 inch from the tip and without involvement of the epithelium The submaxillary glands on both sides were enlarged The nodule on the tongue gradually increased in size when partial excision was performed The healing of the wound was apparently complete, although there remained a deep-seated induration toward the median line Later the superficial epithelium became involved with subsequent formation of a crater-like ulcer, at the same time pain—previously an unimportant feature—became most pronounced, and the patient showed rapid failure of nutrition One week later the anterior third of the right half of the tongue was excised, with no further recurrence The diagnosis was confirmed by the microscopic findings, and tubercle bacilli were isolated in pure culture from an excised lymph-node

(7) In 1912 von Ruck<sup>8</sup> reported a series of 19 cases, 6 of which gave histories of trauma by carious teeth, tongue biting, and in 1 injury from a fish bone In 4 cases the seat of origin was apparently in the deeper tissue, starting in two instances with tumor-like conglomerate tubercles which at first did not involve the mucosa In 1 case a deep abscess formed He reports good results in 4 cases that were treated with watery extracts of tubercle bacilli Four or 5 of his cases were living and in good health, showing no relapse of either pulmonary or tongue lesions after periods of fifteen, twelve, and six years respectively since discharge

(8) Murphy,<sup>11</sup> 1913, reported a case of tuberculoma of the tongue which he found difficult to classify Both the Wassermann and tuberculin test were negative The tumor was near

the midline and went down well into the base of the tongue, and seemed to be situated in the muscularis. A portion was removed for microscopic examination by two or three pathologists and pronounced by them to be tuberculoma. Typical miliary tubercles were found on the surface of the mass.

His other case of tuberculosis of the tongue showed ulcers on both sides. The patient was a man aged fifty-three years. The first lesion appeared two years previous to examination. When seen by the author there were small ulcers all over the tongue, which was enormously swollen, so that the patient could not talk. In both cases tuberculin treatment was used as patients refused operation. Murphy says, "Repair will necessarily be slow, as is always the case when muscle tissue is the seat of the tuberculosis."

(9) Trimble,<sup>18</sup> 1914, reported 2 cases of primary tuberculosis of the tongue. In the first case tubercle bacilli were found in the tissue. A guinea-pig was inoculated with some of the macerated material and developed tuberculosis within two months.

In the second case there was a small bleb on the tongue which ruptured and refused to heal. The ulcer gradually increased in size, and laryngitis developed within about four months. Tubercle bacilli were found in the sputum which was thought to have come from the laryngeal lesion.

(10) Blanchard,<sup>19</sup> 1915, reported 3 cases of secondary tuberculosis of the tongue from the records of the Vanderbilt Clinics. The histopathology of 1 case showed tuberculous structure.

(11) In 1916 Scott<sup>20</sup> collected in the literature 231 cases of tuberculosis of the tongue, 26 of these were reported in America (the first by Toland,<sup>3</sup> of San Francisco, in 1859). Scott's case was a young man of thirty-two years who had noticed a small elevated white area on the left border of the tongue. A small portion of the ulcerated area was excised for microscopic examination. The sections showed tubercles, giant-cells, and round-cell infiltration and tubercle bacilli were demonstrated in the tissue. He mentioned as an interesting observation in the case the existence of the lingual lesion for a period of four



years, during which time the patient was repeatedly examined for pulmonary tuberculosis, with negative result. In the 231 cases collected, tubercle bacilli had been found in 42 cases. There were 26 cases of primary disease, and 6 of these were of the papillomatous type.

(12) Durante,<sup>21</sup> 1916, collected 5 cases from the Mayo Clinics. Three were secondary and 2 primary, at least no other evidence of tuberculosis could be found clinically. Four of the cases were of the ulcerative type and in each the regional glands were involved.

The lesion in the nodular type showed no change for ten years previous to examination and operation. In the 5 cases the histologic diagnosis could be made during the operation by means of frozen sections and the histologic findings decided the course to be taken in the operative and the therapeutic treatment. Durante summarized the histologic picture by stating that "the findings did not differ materially from those of tuberculous lesions seen in other organs, particularly in striated muscle. The fact that extensive perivascular infiltration was found in every case seems to indicate that hematogenous infection plays a prominent part in the propagation of tuberculosis of the tongue."

(13) Taddei,<sup>22</sup> 1922, reported a case of primary tuberculous abscess of the tongue. The nodule had existed two months, when it ulcerated and was removed. A guinea-pig inoculated from the material succumbed to tuberculosis. No other manifestation of tuberculosis could be discovered in the patient, who was fifty-two years old.

(14) Fantozzi,<sup>23</sup> 1923, reported the case of a woman aged fifty-two years whose father had died of pulmonitis and she worked with a nurse who had tuberculosis. Prior to the tongue lesion the patient fell, bruising the lips and cheek, which were soon very much swollen, closing the eye on the injured side. She was not certain if there was an injury to the tongue at this time, but very soon afterward noticed a small seed-like nodule near the tip of the tongue in the midline. At first there was no pain, but later the nodule ulcerated, and as it grew larger became very painful. The tumor grew to the size of a small nut,

the center was elevated, and the edges smooth on the dorsal surface. The mass at first was hard, extending to the under surface of the tongue, and was covered with a whitish material. A small opening was seen on the under surface sufficient to admit the passage of a small probe. A diagnosis of cold abscess was made. Material from the abscess cavity was injected into a guinea-pig, and within fifteen days the pig died of acute miliary tuberculosis which was readily demonstrated in the liver, spleen, and other organs. Tubercles and round-cell infiltration were seen in the tissue sections from the tongue of the patient.

(15) Handfield-Jones,<sup>10</sup> 1923, reported 5 cases of tuberculosis of the tongue seen in general hospital practice within two years.

(16) Morrow and Miller,<sup>7</sup> 1924, reported 16 cases of tuberculosis of the tongue, 2 of the cases they considered primary. One case was that of a man thirty-two years of age, who was apparently in good health. A pea-sized, slightly indurated, non-painful ulcer appeared on the edge of the tongue just to the right of the midline. The pathologic diagnosis was tuberculosis, and roentgenograms of the chest revealed acute miliary tuberculosis. The tongue remained well until the patient's death two months later.

The other case, a man aged thirty-five years, had a lesion the size of a lima-bean, one-half of the lesion was ulcerated and had a cartilaginous base. The right anterior portion of the tongue was excised. The microscopic examination showed the presence of tuberculous structure and tubercle bacilli, but no other signs or symptoms of tuberculosis were found.

(17) Finney and Finney,<sup>4</sup> 1925, in a very concise and complete description of this disease, reported 15 cases observed over a period of twenty-one years, none of the cases had been reported previously. Ten cases had been house patients in the Johns Hopkins or the Union Memorial Hospital. The other 5 cases were observed in the Out-patient Dispensary of the Johns Hopkins. At least 4 of their cases were primary, and perhaps 5 cases. The diagnosis was confirmed by microscopic examination in 10 of the cases, and not stated in the other 5. On the assumption that they were carcinoma, 3 of the cases were op-

erated upon In 4 cases the tongue lesion was the means of bringing the patient to a doctor, and thus led to the discovery of a most extensive tuberculosis previously unsuspected

**Case Reports**—To the above I wish to add 2 additional cases, not previously reported

I am greatly indebted to the patient, a physician, for the privilege of reporting the first case



Fig. 209 —Large tubercle and giant cells

Through the courtesy and kindness of Dr. Rudolph Matas I have the pleasure of reporting the second case

**CASE I**—Male, aged forty three years Family history negative as to tuberculosis He had pneumonia at the age of seventeen years, and a severe attack of influenza in 1918 He smokes a pipe and cigars, but there is no history of injury to the tongue and no carious teeth adjacent to the lesion

In February, 1923 the patient noticed a small mass on the dorsum of the tongue in midline about 1 inch from the tip. A brother practitioner thought it was a cyst, which he incised, and found that it contained blood only. The incised wound healed completely.

In April, 1923 he consulted Dr. Frederick W. Parham, who, fearing the growth might be malignant, attempted to excise it. Dr. Parham described the lesion as "a small globular mass about the size of a filbert, situated in the substance of the tongue in the midline about  $\frac{1}{2}$  inch from the tip." This seemed

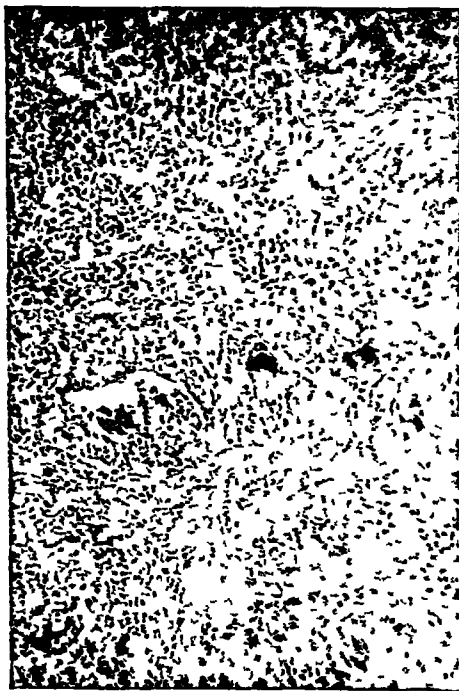


Fig. 210.—Caseation and giant-cells

to be a distinctly circumscribed tumor, and an attempt to excise it was made, but the tumor broke down and apparently was not completely removed."

The excised mass was referred to me for microscopic examination. The sections show typical tuberculous structure. Figures 209 and 210 show different areas of the diseased tissue. In each tubercles, giant-cells, and caseation is seen.

The patient consulted other physicians, who also saw the mounted tissue, and all concurred in the diagnosis of tuberculosis. He writes that following the removal of the mass ulceration occurred, which extended in different directions until practically the entire dorsal surface of the tongue

was covered. The ulceration lasted for almost twelve months. The regional glands have not been involved and there has not been at any time evidence of tuberculosis elsewhere. One physician interpreted the roentgenograms of the chest as tuberculous, but all of the other physicians thought the shadows were due to scarring from pneumonia and influenza. Pictures of the chest are made about every three months and no change has been observed. The patient weighs at this time 176 pounds and says he always gains when idle.

The treatment consisted of Roentgen-ray applications for about every two to three weeks from June, 1923 to September, 1924, when radium was substituted. Radium was applied about every ten days until March, 1925, when the ultraviolet ray was added to the radium treatment.

A recent letter from the patient states that the mass has entirely disappeared and that there is only a very small ulcer about the size of the point on a lead pencil, but that he expects to report a permanent cure within the year.



Fig. 211 —Tubercles beneath the normal epithelium

CASE II — A man, aged sixty six years, a farmer, was admitted to Touro Infirmary August 8, 1918. The parents were dead, mother had laryngitis, and 2 wives died of tuberculosis. The patient had the usual diseases of child-

hood, typhoid fever, yellow fever, and several attacks of malaria, but no history or clinical evidence of tuberculosis

A small ulcer appeared on the tongue near the tip in December, 1917, which soon disappeared, but returned within a few weeks. The first ulcer was not painful, but when it recurred was very painful, so much so as to interfere with eating. In February the ulcer was excised by the late Dr Gilman Winthrop, Mobile, Ala., who described it as "an ulcerative and indurated area." The excised mass was not examined histologically (the doctor having been called into service). The Wassermann was negative,



Fig 212—Round-cell infiltration and caseation

although there was a suspicious history of syphilis. The patient had no further trouble after the removal of the ulcer for about three months. Three weeks ago there was a recurrence and patient was referred to Dr Matas. A preoperative diagnosis of carcinoma was made. Under local anesthesia a large strip of the tongue, dorsum and under surface, was excised, including a large area of seemingly healthy tissue, together with the submaxillary glands. Patient was discharged, improved, eleven days after operation.

Report from the pathologist, Dr Chas W Duval, was tuberculosis of the tongue and tuberculous adenitis of the submaxillary glands.

Information has just been received that the patient died within the year following operation, but cause of death could not be ascertained

Figures 211 and 212 show beautiful tubercles In Fig 211 the tubercles are seen just beneath the normal epithelium More advanced tubercles with caseation and giant-cells are seen in Fig 212, as well as distinct round-cell infiltration

**Summary**—1 Apparently there are more cases of tuberculosis of the tongue than are recorded In the discussion of papers not infrequently other cases are mentioned, yet these cases are not reported in such a way as to be available for statistical study

2 Necropsies, in the majority of instances, are done so hastily as to overlook tongue lesions unless they are pronounced

3 Histopathologic examination establishes a certain diagnosis and should be resorted to Carcinoma was suspected in both of my cases, and in many others that have been reported

4 Early diagnosis of carcinoma of the tongue gives the patient his only chance of a cure, and this is apparently true in the case of primary tuberculosis of the tongue

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# CLINIC OF DRS TALBOT A TUMBLESON

AND

JOHN L CARMICHAEL

CHARITY HOSPITAL

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## CERTAIN APPLICATIONS OF THE VAN DEN BERGH AND FRAGILITY TESTS

DR TUMBLESON We bring before you this morning 2 cases to illustrate certain clinical applications of and correlation between the van den Bergh and fragility tests By the van den Bergh test we mean the application of the Ehrlich diazo-reaction to the detection and estimation of bilirubin in the blood-serum by both the direct and indirect methods as described by van den Bergh in his article in the Presse médicale, June 4, 1921 By "fragility test" we mean the measuring of the resistance of red cells to hypotonic sodium chlorid solution by the method used by Ribiere and Chauffard, a method which has, we believe, come to be used generally in this country. We shall now have briefly the history and physical findings in the first case

CASE I —Mrs G, serial case No C07022, white, aged fifty-five years, was admitted to the Charity Hospital April 11, 1925 The patient came in complaining of weakness, dizziness, and shortness of breath These symptoms began six months previous to her admission She was able to do her housework until three weeks before coming to the hospital, although she had noticed progressive loss of strength She stated that her friends had noted some change in the color of her skin several weeks prior to admission

Physical examination, as you can see, reveals a rather obese white female weighing approximately 170 pounds Her skin is of lemon yellow color and the mucous membranes are pale and anemic Pupils react to light and distance, but knee-jerks cannot be elicited The thorax is symmetric and the lungs are negative The heart is enlarged slightly to the left and there is a systolic murmur at the apex.

The abdominal wall contains much subcutaneous fat There is no evidence of fluid in the peritoneal cavity The spleen is much enlarged, extending to within 1 cm. of the midline and 9 cm. below the costal margin in the left

midclavicular line and 7.5 cm below the costal margin in the left anterior axillary line. It is smooth and rounded and slightly tender on palpation. The liver is enlarged to four fingers below the costal margin in the right midclavicular line.

We have here, then, a patient presenting symptoms—a marked pallor of the mucous membrane and the yellowish discoloration of the skin—suggesting pernicious anemia. We shall now proceed to a laboratory study of the case, using the laboratory reports which we have before us. Turning to the discoloration of the skin, we are at once confronted with the question as to whether or not this discoloration is true jaundice. Have we a means of answering this question?

STUDENT We might examine for bile in the urine.

DR TUMBLESON You assume that if a concentration of bile in the blood is sufficient to cause its excretion by the kidneys, it will be sufficient to cause jaundice.

STUDENT I suppose that is true, although I am not sure that it is so.

DR TUMBLESON Will you tell me, then, what is the threshold for excretion for bile in the urine?

STUDENT I do not know.

DR TUMBLESON Many writers, among whom are van den Bergh, de Takats, and Botzian, have determined by experiments that it is approximately in a concentration of 1 part of bile, or rather of the bile-pigment, bilirubin, to 50,000 parts of blood. This is eight times the normal concentration. This is true only for cases of obstructive jaundice and is dependent on a certain deviation of this concentration, for de Takats has shown in the sudden increase of bilirubin, the blood in biliary colic may give a concentration above 4 units and yet no excretion occur. There seems to be no excretion of bile in the urine in cases of non-obstructive jaundice.

Now what is the concentration of the bile in the blood at which jaundice first appears? I am sorry that that cannot be answered at present. We do know, however, that this depends a great deal on the duration of the concentration. There may be, as one worker has shown, a concentration of over 4 units

and yet no jaundice, while with considerably less concentration jaundice may be rather marked if this concentration has been long maintained. We may say, then, that the presence of bile in the urine is very definite evidence that a discoloration of the skin is due in part or wholly to jaundice. The converse of this, however, is not true, for jaundice may be present long before the concentration is sufficient for excretion of the bile in the urine and, indeed, in certain types of jaundice bile does not appear at all in the urine. Now, is there not a test by which we might estimate the concentration of bilirubin, the characteristic bile-pigment, in the blood?

STUDENT I do not know of such a test.

DR TUMBLESON Well, there are several such tests. Probably the most accurate and practicable of these tests was brought out by Hjams van den Bergh in 1913. Van den Bergh was the first to apply the Ehrlich diazo-reaction to the detection of bilirubin in the blood-serum. He later described an artificial standard easily prepared and very staple, if kept in two separate solutions until time of using, by which a quantitative estimation of the concentration of bilirubin in the serum could be made colorimetrically.

Taking up now the laboratory reports, we find that our patient's serum gave a reading of 10 units concentration of bilirubin. I must explain that 1 unit represents a concentration of 1 part of bilirubin to 200,000 parts of blood. I should state also that the concentration of bilirubin in normal human serum varies between 1 to 1,000,000, that is, 0.2 unit, and 1 to 100,000, that is, 0.5 unit.

Now we may conclude that the discoloration of the skin in this patient is most probably due to jaundice, and that this conclusion is made practically certain when the duration of the condition is taken into account.

STUDENT If this patient should have pernicious anemia, are we to conclude then that, in addition, she has some obstruction to her biliary system, giving rise to jaundice?

DR TUMBLESON That question leads us to a very important subject, that of the causation of jaundice, and I shall ask

you now your idea as to the mechanism of the production of jaundice

STUDENT Jaundice is, I believe, due to the absorption of the bile-pigment, bilirubin, into the blood-stream after it is dammed back into the bile-ducts from obstruction. There is also a jaundice due to sepsis, which I suppose is not necessarily due to obstruction of the bile passages.

DR TUMBLESON You have admitted, then, by your last statement that there is possibly a non-obstructive type of jaundice, and now I may reply to your question of a few minutes ago that possibly this is the type of jaundice which exists in pernicious anemia.

STUDENT There are, I believe, an obstructive and a non-obstructive type.

DR TUMBLESON You are right, and as we shall see later we may subdivide the last type. We must examine now more carefully into the nature of these main types of jaundice. I shall open this discussion by asking you if there is more than one kind of bilirubin.

STUDENT I believe there is only one form of bilirubin, although this is readily oxidized into other pigments, one of which is biliverdin.

DR TUMBLESON What you say about the oxidation of bilirubin is correct. There is now evidence, however, that there are actually two kinds of bilirubin. The first kind of bilirubin, or bilirubin A, as we shall call it, is thought to be produced when hemoglobin is broken down into an iron-containing portion and an iron-free portion. The latter you have learned to call hematoidin, and you have learned that it is formed wherever in the blood-stream or tissue there is hemolysis of red cells. You have been taught to observe its manifestation in the yellow discoloration following a few days after a bruise. It is now thought by some that this hematoidin is identically bilirubin A. Where, have you been taught, is bilirubin formed?

STUDENT In the liver cells and excreted through the bile radicles and finally into the common bile-duct and duodenum.

DR TUMBLESON That is a generally accepted view. A considerable difference of opinion, however, has arisen over the question as to whether the liver cell takes part in the elaboration of all the bilirubin contained in the body under all conditions, especially the condition of jaundice. Some still answer that question in the affirmative, but van den Bergh has now a large following in his view that this bilirubin A, which we have mentioned, is formed elsewhere in the body, wherever in the reticulo-endothelial system red blood-cells are destroyed, whether in the spleen, bone-marrow, or blood-vessels. Thus they believe to be accomplished without the intervention of the liver cell. According to the viewpoint of this group, this type is formed at all times in health and disease, and when the liver is functioning normally this bilirubin A undergoes a slight change in the liver cell to become the second type of bilirubin, which we shall call bilirubin B. Now if excessive concentration of either kind of bilirubin in the blood leads, as it is assumed to do, to jaundice, we may appreciate readily that there are, according to this view, two distinct types of jaundice. There may be a jaundice due to blocking of the bile radicles or ducts and subsequent absorption into the blood-stream of bilirubin B. This, as you see, would fall in your classification under obstructive jaundice. Now there may exist some condition that permits or causes the excessive concentration of bilirubin A in the blood-stream or tissues. This would constitute the non-obstructive type of jaundice. The conditions which may lead to the increase of this type of bilirubin are only two: (1) a hemolysis of red cells so rapid that the normal liver cell cannot change all the bilirubin A into bilirubin B as rapidly as it is formed, and excrete it, (2) a loss of function of the liver cell from toxic or other condition, so that the bilirubin A formed by normal hemolysis cannot be changed and excreted rapidly enough to prevent abnormal concentration of it in the blood-stream. Cases of hemolytic icterus would illustrate the first type of this non-obstructive jaundice, while cases of toxic hepatitis, as from arsenic poisoning, would illustrate the second type. Now the practical question arises, Are we able to differentiate first of all between

these two main types of jaundice the obstructive and the non-obstructive types? I may answer We can In meeting this requirement the van den Bergh test confers a great boon on the clinician, for it seems that with its help we not only can detect jaundice before it appears, so to speak, but we can also tell whether this jaundice or this increase of bilirubin is due to obstruction or not

After the indirect reaction has assured us that there is a pathologic increase in bilirubin, we turn to the direct reaction. If it is a prompt reaction, we conclude that the increase of bilirubin, or the jaundice, is due to obstruction If it is delayed or negative, we conclude that the increase of bilirubin, or jaundice, is non-obstructive How shall we now apply this knowledge to our case?

STUDENT Having learned from the indirect test that bilirubin concentration is increased greatly above the normal, we should now do the direct test

DR TUMBLESON Correct That has already been done We find a notation that the direct reaction was delayed I may tell you that not only was the direct reaction delayed, but that it failed to appear in twenty-four hours What type of jaundice, then, has our patient?

STUDENT She certainly has the non-obstructive type

DR TUMBLESON Yes, certainly We must now attempt to find out whether this non-obstructive jaundice is due to excessive hemolysis or to a lack of function of the liver cell How may we determine this?

STUDENT For one thing, we may examine for bile in the feces

DR TUMBLESON Yes Knowing that there is no obstruction from the result of our van den Bergh test, the absence of bile in the feces would indicate to us dysfunction of the liver cell, while excessive bile-pigment would suggest hemolysis The amount of these, however, is difficult of accurate estimation in the feces We would also possibly find excessive quantities of urobilinogen in the urine if the condition was due to excessive hemolysis What other tests would you suggest that might throw light on this subject?

STUDENT We might test for the resistance of the patient's red blood-cells

DR TUMBLESON Certainly We do this usually by determining the point of beginning hemolysis and also the point of complete hemolysis when using hypotonic salt solution of gradually decreasing strengths Normal bloods show beginning hemolysis usually at 0.42 to 0.40 per cent. sodium chlorid with an occasional blood showing hemolysis at 0.44 per cent. and an occasional one failing to show it till 0.38 per cent. is reached Complete hemolysis of normal blood takes place usually at from 0.32 to 0.28 per cent

Turning to our laboratory reports, we find that this test has been done on our patient's red blood-cells Hemolysis begins at 0.48 per cent. and is complete at 0.34 per cent. What are we to infer from this finding?

STUDENT That the jaundice is due to excessive hemolysis of the red cells

DR TUMBLESON That is quite true Now when I tell you that the blood-picture on this patient at the time of her admission was total red cells 917 000, hemoglobin 30 per cent., anisocytosis, poikilocytosis, 3 nucleated reds to 100 white cells, stippling, polychromatophilia, and a color-index of 1.6+, will you venture a diagnosis?

STUDENT It looks very much as if it is a case of pernicious anemia

DR TUMBLESON Yes It looks like pernicious anemia, but there are two opposing facts First of all, a spleen so large as this patient has is not usually present in pernicious anemia, and, second more important still, there is a decrease of the resistance of the patient's red cells to hypotonic salt solution That makes the diagnosis more clear We believe it to be a case of hemolytic icterus Dr Carmichael will now present to you the other case

DR CARMICHAEL We shall give you immediately a brief history and the significant physical findings



CASE II—R. M., serial No C09265, a colored male, aged fifty five years, was admitted to the Charity Hospital May 12, 1925. The patient's complaint is weakness. This was first noticed several months ago. He lost strength gradually until three weeks ago, when he became considerably worse and had to go to bed. He has been confined to bed practically all the time since. Patient's appetite is good. Urinary history normal. Bowels move twice daily. No history of sore tongue or diarrhea was elicited, but a note about the mental condition of the patient makes such negative statements of little value.

Physical examination reveals a colored (mulatto) male lying in bed, fairly well developed, but rather poorly nourished. Musculature flabby. His skin is greenish yellow in color and only fairly elastic. There is no edema. Lungs show nothing abnormal. The area of cardiac dullness is enlarged slightly to the left and there is a soft systolic murmur at the apex, not transmitted. In the abdomen the liver and spleen are not palpable and there are no areas of tenderness and no masses.

The blood-picture is: total red cell count 615,000, hemoglobin 15 per cent, color index 1.2+, total white count 2500, with 64 per cent neutrophils, anisocytosis, poikilocytosis, 3 nucleated reds to 100 white cells, polychromatophilia, and stippling. Hematocrit reading is 1 part of cells to 14 parts of whole blood. Gastric analysis showed free hydrochloric acid 0, total acidity 35.

What does this case suggest to you?

STUDENT I think of pernicious anemia, but I think that we must rule out malignancy.

DR CARMICHAEL You are right, and an attempt has been made to rule out carcinoma. A gastro-intestinal examination by Roentgen ray fails to reveal any evidence of neoplasm of these regions. An examination of the prostate and the genito-urinary history seems to rule out malignancy of this system. The size of the liver and the absence of a mass in the abdomen are against liver or pancreatic tumor. In a negative way these findings, then, point to pernicious anemia or, we must not forget, to hemolytic icterus. What other examinations might we make?

STUDENT It would be interesting to know the van den Bergh findings.

DR CARMICHAEL Certainly it would. I will give them to you. The indirect reaction shows 3.1 units. The direct reaction shows a delay of two hours. Do you think now the greenish-yellow discoloration of the skin is jaundice?

STUDENT I suppose it is

DR CARMICHAEL Yes, and what type of jaundice is it?

STUDENT It must certainly be non-obstructive

DR CARMICHAEL Yes, and do you see now that we have further evidence against the diagnosis of neoplasm of the pancreas or liver as the cause of this anemia? The jaundice due to such neoplasms is obstructive in type I should call your attention here to the view of certain authors that the bilirubin content of the blood in secondary anemia is never above normal Recently Andrewes, in support of this view, has reported 6 cases of secondary anemia, none of which had increased bilirubin content. If this be true of the secondary anemia resulting from malignancy, we have then in the van den Bergh reactions a valuable means of differentiating malignancy from pernicious anemia and hemolytic icterus, for always in these anemias the bilirubin content is elevated, usually to a concentration of 3 to 5 units in the former and to even higher concentrations in the latter In this case we have still to differentiate between these two anemias How shall we prove that this case is not a case of hemolytic icterus?

STUDENT The spleen is not enlarged

DR CARMICHAEL That is strong evidence, for, as you know, in this condition it is the spleen, representing as it does the largest single division of the reticulo-endothelial system, that hypertrophies to carry on its work of destruction, yet we shall want more conclusive evidence

STUDENT We should do a fragility test

DR CARMICHAEL I will read you the results of this test. Hemolysis begins at 0.36 per cent sodium chlorid and is complete at 0.24 per cent This, then, is not a case of secondary anemia, nor is it a case of hemolytic icterus We are justified in making the diagnosis of pernicious anemia, for in this condition instead of having an increased fragility, one finds a normal or diminished fragility

I must ask you one more question We have a case here presenting a concentration of bilirubin in the blood of six times normal strength and we have found further that the cells are

less fragile than normal. What type of non-obstructive jaundice do you judge this to be?

STUDINI: It is not a hemolytic jaundice, and I suppose, therefore, it must be due to disturbed liver function.

DR. CARMICHAEL: No, that conclusion is probably not correct. You have overlooked one possibility. It is true that the red cells are more than normally resistant to hypotonic sodium chloride solution, yet it is not impossible that the toxin causing the disease, pernicious anemia, is strong enough to destroy these cells in spite of increased resistance. This, we believe, is the true explanation of the findings of the van den Bergh and fragility tests in pernicious anemia. We cannot, however, at this time prove conclusively the incorrectness of the view you have stated.

We hope we have made clear to you the clinical application of certain features of the van den Bergh and fragility tests.

# CLINIC OF DR DANIEL N SILVERMAN

## TOURO INFIRMARY

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### CHRONIC BACILLARY DYSENTERY LIVER ABSCESS FOLLOWING TREATMENT OF AMEBIC COLITIS SOME NOTES ON THE USE OF STOVARSOL IN AMEBIC DYSENTERY

THE presentation of these few cases of chronic bacillary dysentery is made with some hesitancy, since several large series have been carefully studied by clinical as well as bacteriologic means. The purpose of this report, however, is to call your attention to the fact that we are encountering cases with chronic dysenteric symptoms which have been unrecognized bacillary infections over a long period of time. Many such individuals are usually subjected to several diverse and misdirected courses of treatment. Especially is this true relative to the administration of drugs that are used in endamebic disease. Such measures are not beneficial in the least and perhaps sometimes irritating in the presence of bacillary dysentery. The early diagnosis of the latter condition promises quicker and better results in every case.

CASE I —This young man, twenty-five years of age, was seen in October, 1924. He complained of severe abdominal cramps which were accompanied by diarrhea and a gradual loss of 20 pounds in weight. The symptoms had started six months previously. He had noticed some rise in temperature each evening. On examination this man appeared very listless and somewhat undernourished. His temperature was 100° F. The physical examination was otherwise negative.

Proctoscopy revealed the presence of a few small but discrete ulcers of the sigmoid. Smears made from the bowel exudate and repeated microscopic analyses of the stools did not show any ameba or other protozoa.

The blood serum agglutinations were positive for the Flexner dysentery bacillus. Stool cultures contained this organism, which was, in turn com-

pletely agglutinated by the patient's serum. On February 3, 1925 the blood agglutinations remained positive.

At the present time (August 20, 1925) this man is clinically improved, having gained 20 pounds in weight. He states that there is a very occasional tendency to have two or three bowel movements in a day. He has not had any fever in several months.

**CASE II**—The case of this man is somewhat unusual and differs from the preceding individual because he represents a combination of bacillary dysentery and paratyphoid fever. He was referred to me by Dr. Rudolph Matas, who was of the opinion that the fever was not caused by the chronic dysentery of four months' duration. Three months after the onset of dysenteric symptoms, including abdominal cramps and frequent stools containing blood and mucus, his temperature rose to 103° F. Following this rise the fever persisted and ranged from 99° to 101° F. The bowel condition had been relieved by various treatments, including several injections of emetin hydrochloric. He was seen by Dr. Matas and myself during the third week of his febrile condition. The bowels were at that time rather constipated. Repeated blood counts showed a leukopenia, total white blood cells ranging from 3500 to 5850. A proctoscopic examination revealed numerous small round bleeding ulcers of the sigmoid mucosa. The blood culture was negative after seventy-two hours. Blood serum agglutinations were positive for *Bacillus paratyphosus alpha* up to dilution of 1:240, and for Flexner's bacillus up to dilution 1:240, and for Shiga bacillus in dilutions 1:40 and 1:80. These findings assured us of the diagnosis of paratyphoid fever superimposed in chronic bacillary.

**CASE III**—This young woman, aged twenty-eight, represents a severe type of chronic bacillary dysentery notwithstanding the persistence of symptoms for the past four years. When first seen (June 25, 1925) she complained of having rather violent attacks of diarrhea once every two to four weeks. The stools would number from five to ten daily, the temperature rising as high as 102° F. She had lost 20 pounds in weight during the past three weeks.

On previous occasions she had had many treatments for amebic colitis, but *Ameba histolytica* had not been found. The appendix was removed in 1923 in an attempt to relieve the symptoms. The proctoscopic appearance of the mucosa was an intensely inflamed condition with numerous irregular bleeding ulcers.

The physical examination showed a well developed but only fairly nourished woman. The pulse was persistently rapid, from 90 to 110 per minute during rest. The heart was not enlarged. A systolic murmur was heard at the apex and the heart sounds were muffled. The lungs were negative.

There was a low metabolic rate reading of 20 per cent. The blood Wassermann reaction was negative. The urine was normal.

Smears made from the bowel ulcerations and stool examinations did not reveal any protozoa. Tubercle bacilli were not found. The intracutaneous tuberculin reaction was negative. On July 3d the blood serum agglutinations

were slightly positive in dilutions 1:80 for the Shiga bacillus, and complete in dilutions 1:40 and 1:80 for the Flexner bacillus

The patient was put at complete rest in bed with a non-irritating diet of 3000 calories daily. The only medication consisted of 20 grains each of kaolin and charcoal, three times daily. Two weeks later the blood-serum agglutinations remained the same. When last heard from (September 15, 1925) the patient had gained 10 pounds in weight and had only two stools daily, without tenesmus or the passing of blood and mucus.

**Discussion.**—The occurrence of chronic bacillary dysentery, at least in this part of our country, is not unusual. In fact, its frequency is apparently not appreciated. While the great majority of dysenteric cases that we encounter are amebic in origin, many of such cases are bacillary infections. I believe the coexistence of these two conditions is sometimes accountable for our failure to obtain complete cures of individuals who have had amebic dysentery and very adequate treatments for same. Courlet has noted positive agglutinations for *Bacillus dysenteriae* of the blood-serum of a fair proportion of amebic cases. Houghwont has found that many normal individuals without histories of dysentery give positive agglutination reactions for *B. dysenteriae*. He, therefore, relies upon microscopic analysis of the bowel exudate for a specific or differential diagnosis. Notwithstanding such observations, a positive agglutination for *B. dysenteriae* in dilutions above 1:40, in the presence of definite symptoms, justify the diagnosis of bacillary infection and the institution of appropriate treatment. The selection of the specific bacillus of the dysentery group by agglutinins is impossible in serum agglutination under 1:250.

In a large local institution, where numerous cases of amebic colitis are constantly under observation, only 12 patients during the past five years have had a diagnosis of chronic bacillary dysentery. There was not a single case showing presence of both diseases in the same individuals. Seven of this small group of bacillary dysenteries were so termed from the clinical signs alone, whereas the other 5 were diagnosed from positive serum reactions. In only 2 of the series were stool cultures undertaken, and with negative results. One would ordinarily judge that these 5 cases of bacillary dysentery, properly diagnosed as such,

in a first-class institution with excellent laboratory facilities in this part of the country, must represent only a small proportion of such cases encountered

The treatment of amebic dysentery with stovarsol has been wrought with considerable success. In a series of cases treated by this comparatively new preparation Johns and Jamison have reported good results in over 77 per cent of 46 cases. It is their belief that stovarsol gives rapid relief, perhaps equal to any other method of treatment.

I have seen complete healing of the amebic ulcers and disappearance of all vegetation and encysted amebæ from the stools in 6 cases. These individuals were given an average of 30 tablets (0.75 gm) in a ten-day period. On the other hand, 10 cases received only symptomatic relief, less frequent stools and diminished tenesmus, in spite of repeating the courses of stovarsol (50 tablets, or 1.25 gm). In 3 of these individuals the ulcers showed no tendency to heal, 2 cases having sufficient stovarsol to bring about a definite arsenical poisoning.

The following case represented an apparent cure of the dysentery after taking 25 tablets of stovarsol (50 gm) within a period of ten days, when a subsequent attack of dysentery within two weeks was soon complicated by the development of a liver abscess.

Captain C. A., a Spanish seaman, forty-two years old, was seen June 1, 1925. He was referred by Dr. Rudolph Matas. The patient complained of having frequent bloody stools and severe abdominal cramps. This condition started about two months previously. He was given some ipecac. He was found to be very much undernourished, weighing 107½ pounds. The physical examination revealed an asthmatic bronchitis which the patient believed was of twenty years' duration.

Proctoscopic examination presented a few small ulcers in the sigmoid.

The stools contained numerous flagellates of the *Chilomastix* and *Trichomonas* species, and *Entamoeba histolytica*.

The patient was placed at absolute rest on a soft diet in the Touro Infirmary. He was then given 3 tablets of stovarsol each day for four days. He insisted upon leaving the hospital, but continued the same treatment at home until he had received 25 tablets. On June 24, 1925 the patient reported slight "weakness in the legs." The bowels had become constipated and required mild laxatives. The stools were found to be free of any parasites or cysts. Stovarsol was then discontinued. Two weeks later, while out at

sea, dysenteric symptoms came on rather acutely. Within a few days he had developed pain in the right upper abdomen and slight rise in temperature. On his arrival in Honduras a diagnosis of liver abscess was made. The total leukocyte count was 22,000, with 89 per cent neutrophils. He was given hypodermics of emetin hydrochlorid, 1 gr each day for twelve days, bismuth subnitrate, 1 dram every four hours for twelve days.

Upon his immediate return to New Orleans the physical examination showed an enlarged liver, palpable about  $2\frac{1}{2}$  inches below the costal margin in the midclavicular line, with a tender mass the size of an egg on the lower border of the right lobe.

On August 7, 1925 the patient was admitted to the Touro Infirmary. The temperature was  $99^{\circ}$  F, total white blood-cell count 10,000, neutrophils 76 per cent. Dr. Matas now directed the treatment with the view of possible surgical interference. On this day 1 grain of emetin hydrochlorid was administered. The following day 2 grains were given. The blood-pressure was now 112/78. August 9th 1 grain of emetin was injected. The mass showed some reduction in size. August 10th, two injections of emetin, 1 grain each, were given over a period of twelve hours. From August 11th to 21st he had 1 grain of emetin daily. There was a gradual but definite reduction in the size of the abscess. The temperature had not gone above  $100^{\circ}$  F during the hospital treatment, quinin sulphate, 3 gr, and strychnine sulphate,  $\frac{1}{40}$  gr, were given by mouth from August 14th to 21st. During the following eight days (from August 21st to 29th) he received injections of emetin 1 grain daily. The entire quantity of emetin administered was 36 grains.

**Summary.**—Whereas the above case represents a complete failure of stovarsol to bring about complete cure of amebic dysentery, this patient is presented to you for the interest surrounding the development of, and consequent cure of a complicating amebic abscess of the liver. Such a complication is very rarely encountered soon after the treatment for dysentery by any of the known methods. The employment of emetin must be carefully guarded, for while repeated doses were effective in a non-operative attempt to combat the abscess in this particular case serious poisoning may result rather unexpectedly.

One is justified judging from current reports, in the use of stovarsol in the treatment of amebic dysentery. I do believe, however, that our patients should be in a state of physical rest and maintaining a non-irritating diet. Should this preparation, which is so easily administered and unobjectionable to the patient, fail to completely cure the case as determined by repeated examinations of the bowel and feces the rather strenuous and disagreeable ipecac methods should be tried.





## CLINIC OF DR J HOLMES SMITH, JR

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#### BISMUTH IN THE TREATMENT OF VISCERAL SYPHILIS

THE work of Sazerac and Levaditi<sup>1</sup> in demonstrating the spirocheticidal effect of bismuth has added another and it is hoped a useful drug to the list of remedies already employed in the treatment of syphilis. Since 1922 numerous investigators, particularly in Europe, have reported their results with this drug, and almost without exception they are very enthusiastic regarding its antiluetic properties.

Soluble and insoluble bismuth salts have been employed but it is generally conceded that the insoluble salts are preferable because of the lessened toxicity, slower rate of absorption, and continuation of the effect of the drug over a relatively long period of time. Two preparations, potassium bismuth tartrate with butyn and bismuth salicylate, have been employed by me. Administration has generally been at weekly intervals, for twelve doses, given deep in the gluteal muscles.

Reports are to be found in the literature of the use of bismuth in all stages of syphilis. The action of the drug, however, appears to be so slow that it would seem inadvisable to use it in any but the later stages of the disease, unless it be as a supplement to a course of arsphenamin. The main field of usefulness of bismuth and its salts appears to be in the later stages of the disease, particularly in those cases presenting evidence of visceral involvement. Especially does it seem to be of value where there is involvement of the central nervous system and in cardiovascular syphilis, the latter group of cases being considered very poor risks for the administration of arsphenamin. It is also claimed that bismuth will frequently bring about a negative

Wassermann in patients who have been Wassermann-fast for arsphenamin and mercury. The cases here presented have been selected to demonstrate its usefulness in another form of visceral syphilis, namely, where there is involvement of the liver, which organ is particularly susceptible to the toxic effects of arsphenamin. Four cases from my series are here presented: 3 of liver disease (2 having a hepatitis and 1 a gumma) and 1 case complicated by an apparently severe kidney involvement.

On theoretic grounds, at least, the 3 cases with liver involvement should be well suited for the administration of bismuth. The fourth case is being presented because of the good results, in spite of the fact that a damaged kidney is considered by some a contraindication to the use of this drug.

CASE I—E. P., a colored (mulatto) female, aged fifteen years, presented herself at the clinic on April 6, 1925 because of a yellowish color to the skin and eyes and very dark urine. She had been sick for two weeks. Examination showed a marked icteric tint to the skin, sclerotics, and mucous membrane of the soft palate. There was a diffuse macular eruption over the skin of whole body. Epitrochlear lymphatics were distinctly enlarged. Wassermann reaction was strongly positive. Urine showed a large amount of bile, albumin 2 per cent. No urobilin.

Van den Bergh test of liver function. Indirect reaction, 21 units. Direct reaction (prompt), 17.5 units, suggestive of both toxic and obstructive jaundice.

Red and white blood cell count showed nothing of note.

Treatment was begun with bismuth, no other medication being employed. Potassium bismuth tartrate with butyn was administered at weekly intervals for five doses, after which bismuth salicylate, similarly administered, was given for six doses. A total of eleven injections of bismuth were given, the patient failing to return for the twelfth dose. Clinical improvement was noted after the third injection. Jaundice became less marked, the urine contained less bile, and the macular eruption was not so pronounced. In addition to this, the patient began to feel very well. May 20th, following the sixth injection of bismuth, the Wassermann was strongly positive, but otherwise there was great improvement. The urine was free of bile and albumin, jaundice was very slight, and the van den Bergh test was: Indirect, 1.6 units. Direct (prompt), 1.5 units.

At the time of receiving the eleventh injection the patient was clinically well. She failed to return for the last injection and, consequently, no study of the blood was made at this time.

This patient was next seen on September 30th, approximately three months after the last dose of bismuth. At this time she felt and looked well, except that there was an injection of the right eye due to an interstitial

keratitis, no doubt of luetic origin. There was no evidence of jaundice and the van den Bergh test showed no retention of bile-pigments. The Wassermann at this time was weakly positive.

CASE II—C T, a colored female, aged thirty-two years, came to the clinic May 11, 1925 complaining of weakness, fever, chills, and loss in weight. She was thin, emaciated, and apparently very sick. The physical findings were negative except for an enlarged liver which presented a large, firm, and painless mass about the center of its free margin. There was no jaundice. The urine contained no bile, urobilin, or albumin, and the van den Bergh test of liver function was negative for retained bile-pigments. The blood showed a moderate secondary anemia. Wassermann test was strongly positive.

Bismuth salicylate was administered at weekly intervals for twelve doses. Clinical improvement was noted early and the patient steadily gained in weight and began to feel exceptionally well. Upon completion of the bismuth administrations there had been a gain in weight of at least 15 pounds, if not more, the patient was in excellent spirits, and the enlarged liver and tumor mass (gumma) were no longer palpable. Following the last injection of bismuth the Wassermann reaction was strongly positive.

CASE III—M B, a colored female, aged about thirty-five years, came to the clinic on June 8, 1925 complaining of being "sick all over," with pains and aches over whole body. The pains were worse at night and had been present for about one year. Nausea was becoming a frequent symptom. There was no vomiting. Recently she had noticed her eyes becoming yellow. There was a history of two miscarriages and no other pregnancy.

The physical examination showed a moderate icterus of sclerae and soft palate. There was a small perforation about center of soft palate. Heart rate was accelerated, but apparently otherwise normal. The liver edge could be felt about 1 inch below costal margin and was sensitive to pressure in epigastrium. No adenopathies were noted. Urine showed a large amount of bile. Urobilin and albumin were also present.

Van den Bergh test of liver function. Indirect, 15 units. Direct, biphasic, indicating both a toxic and an obstructive condition.

The blood showed a total leukocyte count of 10,500 with 80 per cent of neutrophils. Wassermann test was negative upon three separate examinations.

Regardless of the repeatedly negative Wassermann and the moderate leukocytosis, it is felt that a diagnosis of syphilis and syphilitic hepatitis is justified for the following reasons: Pains of a year's duration, worse at night, perforation of the soft palate, two miscarriages, no other pregnancy, results of treatment.

Bismuth salicylate was administered at weekly intervals, a total of seven injections being given. As with the previous cases, improvement was prompt. The jaundice rapidly disappeared, there was no bile in the urine, the pains and aches completely subsided, and she began to feel and look well. After administration of the seventh injection the patient failed to return for further treatment.

CASE IV—H H, a colored female, aged sixteen years, was found to have, in addition to a strongly positive Wassermann, evidence of severe kidney involvement. The urine contained 6½ per cent of albumin and there were many granular casts present. Aside from this there was little of note in her physical findings.

She was given deep injections of potassium bismuth tartrate with butyn, a total of five being administered at weekly intervals. After the fifth dose the Wassermann was negative, the urine no longer showed albumin or casts, and the patient was clinically well. She failed to return for continuation of her treatment.

Discussion—Perhaps the most striking feature about these cases is the marked clinical improvement, both objective and subjective, becoming noticeable about the time of the third bismuth injection and continuing throughout the course of treatment. The patients felt very much improved and all outward evidence of disease disappeared.

The effect upon the Wassermann reaction, however, has not been so pronounced. Of the 3 patients showing strongly positive Wassermann at the beginning of treatment, 1 became negative after five doses of bismuth, one was weakly positive three months after the last dose, and one was strongly positive immediately following the twelfth injection. That the disease in one case at least was only arrested is further attested by the fact that she later developed an interstitial keratitis.

It seems very evident that bismuth has spirocheticidal properties, but it remains for time and extended clinical observation to relegate it to its proper place in relation to arsphenamin and mercury in the treatment of syphilis.

Those who have studied the action of the bismuth salts, both experimentally and clinically, are, almost without exception, quite enthusiastic about them, and all seem agreed that they are much more effective than mercury and only slightly less so than salvarsan, but because of its slow rate of absorption its employment in early syphilis is apparently much less desirable than salvarsan, where a rapid spirocheticidal action is desired.

Hopkins,<sup>2</sup> working with different bismuth salts, says "The values found for these bismuth preparations are far higher than any recorded estimations for arsenical or mercurial drugs tested

in rabbits They are strictly comparable to tests of insoluble mercury compounds and leave no doubt that bismuth is far more effective than mercury under experimental conditions The results are sufficient, however, to convince one that bismuth is, experimentally, a highly effective antisyphilitic agent." Grund<sup>3</sup> claims "Its superiority over mercury, both in its spirocheticidal and serologic aspects is plainly evident Milian in this regard places it midway between the arsenicals and mercury, and compares the therapeutic activity of arsphenamin, bismuth, and mercury in the following manner The therapeutic activity of arsphenamin is represented by the figure 10, that of bismuth 7, and that of mercury by the figure 4" Grund,<sup>3</sup> however, quotes Greer and Muschiatti as follows "Though possessing a definite curative action on specific lesions, bismuth could not replace the arsenicals or mercurials at present in use"

The effect of bismuth upon the Wassermann reaction depends largely upon the type of case and the preparation used and mode of administration In the cases here reported, 2 out of 3 had a positive Wassermann following treatment There are several possibilities to be considered in this regard Were the intervals between injections too long? Was sufficient bismuth administered? In Case II, should several weeks have been allowed to elapse after the last dose of bismuth before the Wassermann reaction was made?

Dr J H Musser (personal communication) believes that had the bismuth been administered twice weekly instead of once a week it would have been more effective in reducing a positive to a negative Wassermann On the other hand, it is claimed by some that because of the slow absorption of bismuth the Wassermann does not become negative until some time has elapsed after administration of the drug Lehner and Radnar report a series of cases in which the Wassermann reactions were all strongly positive at end of course, but all became negative a month after treatment In tabulating 122 courses of bismuth given to patients with positive Wassermann reactions Hopkins<sup>2</sup> found that "a negative test was obtained in 38, or 31 per cent., of the cases In only 1 of the cases which were strongly positive and in 6

weakly positive before treatment were persistent negative reactions obtained "

One of the most striking effects of bismuth treatment at times is its ability to produce a negative Wassermann in cases which have resisted salvarsan and mercury In 2 out of 3 of our cases, however, which were Wassermann-fast to arsphenamin, bismuth failed to alter the reaction

That bismuth is very slowly absorbed after deep muscular injection is very beautifully illustrated by Beinhauer and Jacob,<sup>4</sup> who present radiographic photographs showing bismuth in the gluteal muscles weeks after its injection, and in one case bismuth salicylate was still present nine weeks after administration

In discussing the slow absorption of bismuth Levaditi, Nicolau and Schoen<sup>5</sup> assert "Insoluble bismuth salt, injected intramuscularly, is retained in the muscle tissue for months and is only slowly liberated Because of gradual elimination of bismuth the kidneys are not injured Minimal quantities of bismuth suffice to destroy spirochetes" Hopkins<sup>2</sup> is of the opinion that "there seems little reason for crowding with large doses we get excellent results with relatively small amounts "

That bismuth has toxic properties seems to be well established, though none have been noted in my cases, probably due to the relatively long interval between doses I did, however, see several patients who developed gluteal abscesses following injections of potassium bismuth tartrate with butyn Because of this bismuth salicylate was substituted, and, aside from occasional soreness at site of injection, there have been no further untoward symptoms

Various local and systemic toxic symptoms have been reported They vary from mild stomatitis and gingivitis to severe gastro-intestinal manifestations complicated by nephritis not unlike mercurial poisoning Perhaps the most frequent condition encountered is a black line along the margin of the gums Ordinarily the appearance of this line is not of great significance, but Grund<sup>3</sup> believes that pigmentation plus foul breath should warrant immediate cessation of treatment Most authors report varying degrees of kidney damage, but all

seem agreed that the injury is seldom permanent and generally subsides with cessation of treatment.

It will be noted in Case IV of this series that the patient had evidence of marked kidney involvement which subsided under bismuth therapy

It seems that with judicious administration there is not much likelihood of severe toxic symptoms, and by some the bismuth preparations are considered the least toxic of the spirocheticides

The total dosage for any one course of bismuth is from 2 to  $2\frac{1}{2}$  to 3 gm given over a period of eight to twelve weeks, each dose equaling from 0.1 to 0.2 gm. It probably will be found necessary or advisable to repeat the course of bismuth once and possibly twice, with intervals of from two to four months between each course

**Summary**—In the bismuth preparations we undoubtedly have agents with pronounced spirocheticidal action. If all statements concerning their effectiveness are true, they are almost as valuable as arsphenamin, they are less toxic than mercury, and their effect is continued over a greater period of time than either. If the many reports are only partly true we still have a useful adjunct to arsphenamin and mercury in combating syphilis

In the type of cases here reported its usefulness appears to be very great, if not as a permanently curative agent, at least as a preliminary to the administration of arsphenamin and mercury. When it is borne in mind that arsphenamin frequently exerts its toxic effects upon the liver, even to the point of producing jaundice, it can readily be seen that bismuth is a useful addition to the therapy of such conditions

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# CLINIC OF DR H W BUTLER

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### AINHUM (DACTYLOLYSIS SPONTANEA)

I D, a well-developed negro male, thirty-five years of age, came to the clinic to have his small toe amputated. Three years ago he experienced a burning and itching sensation on the small toe of the left foot. The inside became tender, but without swelling, inflammation, or pain.

Two months ago patient noticed a small fissure at the interphalangeal articulation. It surrounded the toe and became gradually deeper until it had almost amputated the digit. It had become so inflamed that it interfered with his locomotion. Inflammation and pain appeared during the latter period of the disease.

**Definition**—Ainhum, an African word meaning "to saw off," also called "dactylolysis spontanea," is a semitropical and tropical disease of great chronicity, usually occurring in the dark-skinned people. It is confined with rare exception to the male. It is characterized by spontaneous amputation of the fifth toe, with involvement, in some cases, of the fourth. It is a disease of symmetry, amputating corresponding members of each extremity, usually the foot. A constricting band, or line of demarcation, gradually forms at the proximal interphalangeal joint, usually of the fifth toe, deepening its furrow until complete amputation occurs. This is often the only evidence of the disease, and is pathognomonic. In some cases pain is an early symptom and continues throughout the disease.<sup>2</sup>

**Etiology**—Many etiologies have been proposed, none of which are satisfactory. That it is due to irritation, coupled with an individual or racial predisposition, seems to pacify us, but this is far from the solution.

1 A lesion of leprosy. Zambaco Pacha<sup>1</sup>

2 Caused by injuries to the toes by chiggers (*S. penetrans*) Wellman<sup>2</sup>

- 3 Trophoneurosis Matas<sup>3</sup>
- 4 A circumscribed scleroderma Corre,<sup>4</sup> Matas<sup>3</sup>
- 5 A congenital spontaneous amputation Proust.<sup>2</sup>
- 6 Heredity Duhring<sup>5</sup>
- 7 Constricting fibrous tissue Eyles<sup>6</sup>
- 8 Syphilis
- 9 The wearing of toe rings, etc
- 10 Infection Castellani<sup>10</sup>

**Pathology**—The lesions reported have been a hypertrophic thickening of the derma, especially the papillary layer The



Fig 213—Amhum A longitudinal section through the amputated portion of the small toe The upper margin shows the area of the disease Note the inward growth of the epidermis which forms the constricting band The dark area is the remains of bone

skin becomes dry, thick, and tough overlying the diseased area, the blood-vessel walls thicken, and the bone becomes partially or completely absorbed There is a cicatricial formation in the tissues involved, a deposition of fat, and a strangulation necrosis occurs distal to the constricting band

**Laboratory**—Blood Wassermann negative

Urine negative

Acid-fast stains were made of tissue sections, but no acid-fast bacilli were found. Levaditi's stains were also made, but they revealed no spirochetes. Pathologic sections of tissue showed the characteristic epithelial down growth, absorption of the terminal phalanx, thickening of the blood-vessel walls, and fatty degeneration.

*Roentgen-ray Report*—Plantar view—complete absence of the distal phalanx of the small toe.

*Symptomatology*.—It usually begins as a depression, or furrow, at the internal and inferior surface of the root of the small

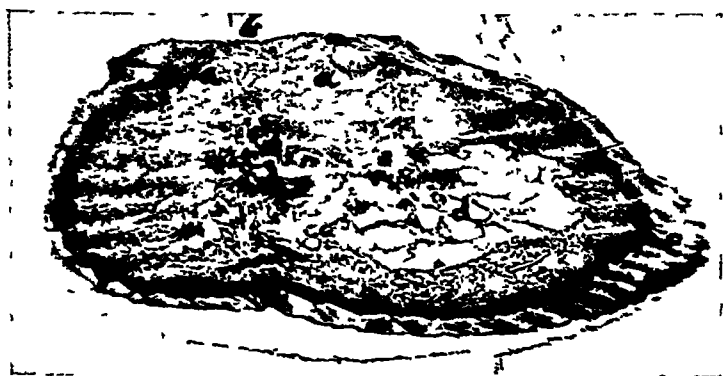


Fig 214—Ainhum. Longitudinal section of the amputated toe. *a*, Thickening of epithelium, forming constricting band; *b*, line of amputation; *c*, remains of bone; *d*, fat; *e*, cornified epithelium.

toe. In the early stages this condition is attended by pain in some cases,<sup>2</sup> and in others it is completely absent. The sulcus, beneath which is a fibrous constricting band, gradually deepens, producing characteristic tissue changes, *i. e.*, down growth of epithelium, endarteritis, fatty degeneration, hypertrophy of the sweat-glands, and absorption of the bone. Late in the disease the toe may ulcerate and pain is a prominent symptom. It may be confined to one small toe, or both, and in some cases attacks the fourth, and in rare cases the fingers may be involved. There is no constitutional condition accompanying the disease in the majority of cases.

Differential Diagnosis —Raynaud's disease Paronychia  
Leprosy

Raynaud's disease is painful and effects most often the upper extremities Paronychia is inflammatory throughout, anhum is not. The trophic lesions of mutilating leprosy are found on any toe or finger, usually on the dorsal side, and other manifestations, past or present, are almost invariably present <sup>7</sup>

Prognosis —The prognosis is good as to life, but the effected member is amputated in from two to ten years The disease may be arrested at this stage, or it may continue until it has amputated several toes of each foot

Treatment —In the early stages, if the constricting band is incised transversely, the affection may be arrested The incision is made to the periosteum It is usually made on the lower surface through the band, but some prefer to make the incision on the opposite side When the disorder is of long duration, amputation of the toe is the only recourse <sup>8</sup>

Comment —The bacillus of Hansen has been found in every tissue of the body except the muscles, and has a special predilection for the skin <sup>2</sup>

Constant injury to the toe over a long period of time, producing an epithelial thickening, or keratosis, is generally agreed to be one of the causative factors

A tissue response to injury in the negro by keloid formation has been mentioned by some

Congenital amputation caused by constricting amniotic filaments during fetal life is not confined to the fifth toe, but may amputate any member Ainhum is not a congenital disease

Heredity cannot be established in all cases <sup>2</sup>

Syphilis has very little clinical and no laboratory evidence to support it

The wearing of toe rings, strings, etc, may in some cases be partially responsible, but rings are more often worn on the fingers, and they are the digits less often affected

The writer also agrees with Matas, that it is a trophoneurosis, the cause of which is not plain

**Conclusions** —Ainhum is a condition in which the etiologic factor is still obscure, and because it is confined almost entirely to the black races there must be, besides constant irritation, some inherent factor which predisposes to the disease

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## THE SCHICK TEST ON STUDENTS

I THOUGHT it might be of interest to you to know the results of the Schick test as applied to medical students to determine their immunity so that they would be able to make rounds in the diphtheria wards

Eighty-four senior medical students, 1 hospital intern, and 4 nurses were given the test. In each case 0.2 c.c. of toxin solution containing 1/50 minimum lethal dose of toxin was injected intradermally on the flexor surface of the right forearm. Controls were made in every case by injecting into the left arm the same amount of the same toxin which had been heated to 75° C for fifteen minutes. This kills the toxin, but does not destroy the protein and does not prevent the so-called protein reaction which may be confused with the specific reaction if the individual was sensitive.

Reactions are best read on the fourth day in order to differentiate true from pseudoreactions. A positive reaction is shown by a sharply defined area of redness measuring from 1 to 2 cm., which usually appears at the site of the injection in from twenty-four to forty-eight hours, but may be delayed until sixty hours. The reaction increases in intensity during the first three or four days, reaches its height on the fourth day, persists for several weeks, and on fading gradually gives place to a brownish pigmentation with superficial scaling.

A positive Schick test means that the individual's blood does not contain 1/30 of a unit of antitoxin per cubic centimeter, which amount has been determined to be sufficient antibodies to protect against the disease. On the contrary, a negative Schick test is evidence that the blood contains the required amount of antitoxin and that the individual is not susceptible to diphtheria.

The Schick test, as you know, was brought forward by Dr. B. Schick<sup>1</sup> in 1913 while working in the Pediatric Clinic of the



University of Vienna under the direction of Prof C von Pirquet The purpose of the test is to determine those who are susceptible to diphtheria and those who are not in any given group

Of the 89 persons tested, 76, or 85.4 per cent, gave negative reactions and 13, or 14.6 per cent., gave positive Schick reactions

**Immunization**—Four of the students who gave positive Schick reactions were immunized with 0.1 lethal plus dose<sup>2</sup> of the toxin-antitoxin mixture given by subcutaneous injections every five or six days for three doses Each injection consisted of a 1 c.c. dilution containing the 0.1 lethal plus dose of the toxin-antitoxin mixture About three months later the same students were Schick tested again and all gave negative reactions This would indicate that the required amount of immune bodies was present in the blood produced by active immunization

**Reaction**—One student, after receiving the second dose of immunizing serum, developed rather severe constitutional symptoms He was in bed for three days with rigor and a fever of 103° F The urine was examined and found negative except for a febrile albuminuria The third dose was not given in this case His immunity was not tested again

A student who suffers with hay-fever experienced an exacerbation of his condition for a period of a week after the Schick test was applied

There were 4 students who gave protein reactions It is noteworthy that one of these had had horse-serum three years before

The intern on the service gave a strongly positive Schick reaction, but was not immunized He made cultures, swabbed diphtheria throats, did tracheotomies, often having children cough and sneeze in his face, but he did not contract the disease

**Summary**—1 Of 84 medical students, 1 intern and 4 nurses, 89 persons in all, 13, or 14.6 per cent, gave positive Schick reactions, 76, or 85.4 per cent., gave negative reactions

2 A hay-fever sufferer experienced a return of his condition after the Schick test was made, which was negative

3 Out of 4 persons immunized with the standard (Park's) toxin-antitoxin mixture, 1 suffered a severe reaction following the second dose. Therefore no larger dose than the 0.1 lethal plus dose should be employed.

4 Three persons who were positive when first tested, and who were immunized, gave negative Schick reactions when tested about three months later.

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# CLINIC OF DR EARL Z BROWNE

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### SICKLE-CELL ANEMIA

WHILE sickle-cell anemia is not a new disease and is also relatively frequent, yet I feel that it is rare enough to justify showing a patient that has only recently come into the Charity Hospital of New Orleans. The case is also interesting because clinically there was present some external signs that bore strong evidence of tertiary syphilis and chronic valvular heart disease and was only diagnosed by a routine blood examination.

Sickle-cell anemia seems to be a disease peculiar to the negro race and has for its chief characteristic a peculiar sickle- or crescent-shape formation of the red blood-cells and a blood-picture in a great way analogous to that of pernicious or primary anemia. Indeed, it appears to be one form of this disease with familial and racial characteristics. In some cases—the so-called latent ones—the only thing found is the erythrocytic abnormality, while in others there is, in addition, recurrent paroxysms of prostration, pains in joints and extremities, some palpitation of the heart, and a more or less tendency to chronic leg ulcer.

Since the first report of a case by Herrick in 1910 there have been relatively few cases cited. Huck and Sydenstricker, however, think the disease fairly common, as in November, 1923 both had seen in their clinics about 40 cases. The latter states that it is prevalent in  $\frac{1}{100}$  of 1 per cent of all negroes examined in his clinic. In New Orleans La., S. Chaille Jamison is the only one who has reported cases, and has, up to the present, 2 on record. It is due to his courtesy that I show this case.

Tom Anderson, a colored male, aged twenty four years, a resident of Plaquemine, La., by occupation a moss picker, came to the Charity Hospital

on September 8th because of feeling weak and due to the presence of ulcers on legs In the admitting room a tentative diagnosis of nutral regurgitation was made, and he was admitted to Medical Ward No 14 Soon after admission he was put on mixed treatment—due to the presence of leg ulcers—and another tentative diagnosis of lues was made On the following day, while in search of material for study in class room, I was impressed with his case as possibly being good material for the study of anemia, and took some smears of his blood

*Complaint*—"Tired, weak feeling Ulcers on my legs"

*Family History*—Father is living, aged sixty-six Has apparently always enjoyed good health, though patient states that he has at times complained of pains in joints and muscles This, however, has not interfered with hard manual labor Mother died with "lung trouble" The age at death of mother is unknown to patient, as he was quite young at the time Four brothers are living and well All are apparently strong Four sisters are living The 3 older ones enjoy good health, but the younger one has always been "puny" like the patient Was in Charity Hospital recently on account of "weakness" One sister died at age of twenty-five during labor Three sisters died in infancy, before the birth of patient Four brothers also died in infancy The living members of the family all reside in Plaquemine, and it has not been possible at the present to examine their blood

*Past History*—Patient states that he had whooping-cough and mumps during early childhood, exact age unknown During his twelfth year he had attacks of chills and fever, which came intermittently over a period of six months Was cured with quinin Measles at the age of sixteen From about the age of two years until the age of sixteen he states that he had frequent attacks of "rheumatism" Had about four such attacks a year, and the usual duration was around ten days During these times he had severe pains in both the lower and upper extremities, lower portion of back and generalized muscle soreness The pains were often so severe that he would be unable to walk or to use hands and had to be fed by members of the family Since the age of sixteen the "rheumatism" has improved a good deal and the attacks have been more transient He has always been considered a "sickly" child and never able to play much with the other children, as he would tire so easily Had influenza three years ago No history of epigastric pains or indigestion, except a slight attack four weeks ago Has noticed that he perspired rather profusely at night Weight for the past five years has been around 110 pounds Denies venereal infections

*Present Illness*—The present illness is dated as beginning about four weeks ago, when ulcers appeared on both ankles and there was an unusual amount of weakness, but it seems to have started with early childhood For the patient says that he has been "sickly" and weak all of his life and has never been able to "pick up any strength" Has never been able to do heavy work, or any kind of work when hurried When attempting moderately heavy work, or on being hurried, he starts to "tremble all over," and has to lie down until it passes off Headaches are frequent, with attacks of dizziness About every day or so has noticed that his heart would beat fast

and that he had spells of shortness of breath. Several times while eating his gums bled a small amount. Pains in both extremities and back have been frequent, but not as severe during the past six years as prior to that.

Four weeks ago he began to have ulcers on legs (one on each ankle) and to feel more weak than usual. So he decided to come to the hospital. The appetite is fairly good, with very little, if any, distress after eating. Thinks he has been having some fever during the past month, especially in the afternoons. Daily evacuation of bowels without the aid of purgatives. Urination day, five to six times, night, one to two. Urine is generally highly colored and there is a slight amount of burning. Smokes cigarettes occasionally. No alcohol.

*Physical Examination*—Reveals a colored male that is poorly nourished and developed and appears very anemic. The temporal fossæ are sunken and the zygomatic arches are prominent. Age is said to be twenty-four, but he appears not over seventeen. There is very little growth of beard, no hair over sternum and the pubic hair is scant. Voice is weak, high pitched and somewhat termulous. Mentally he seems to be fairly alert. Gait is somewhat slow and after walking there is marked dyspnea. On the external aspect of left ankle, just below the malleolus, there is a shallow ulcer with "punched-out" edge, sloughing base, foul odor, and measuring approximately 4 cm in diameter. A similar ulcer is present below the internal malleolus of the right leg. No edema of the lower extremities or back.

Temperature, 99½° F. Pulse 96. Respirations, 20. Weight, 110 pounds. Scalp, ears, and nose are negative.

Both scleræ are of a decidedly greenish-yellow color. Left eye shows divergent strabismus. Pupils are equal and react to light and accommodation. Palpebral conjunctivæ very anemic.

The mucous membranes are very anemic. Tongue is slightly coated. Teeth are all present, but badly discolored. Two carious molars. Slight amount of pyorrhea, with retraction of gums. The right tonsil is adherent and atrophied. Left tonsil somewhat hypertrophied.

Anterior cervical and both inguinal glands are markedly hypertrophied. Epitrochlear glands not felt.

*Thorax*. The supraclavicular spaces are depressed. No definite lagging on deep inspiration. Tactile fremitus is absent at the right base posteriorly and is increased just above area of flatness. The percussion note is impaired at right apex posteriorly and at the right base there is flatness beginning at the level of the tenth dorsal vertebra. This area of flatness extends to the right anterior axillary line, where the upper limit is at the seventh rib.

In this region the voice sounds are distant and occasional mucous and crepitant râles are heard. In a small area 2 inches from the tenth dorsal vertebra there is heard a definite friction-rub.

*Heart*. Apex-beat is visible in the fifth interspace, 9 cm from the mid-sternal line. No thrill is felt. Both the right and left borders of the heart are within normal limits. A pronounced systolic murmur is heard at the apex and increases in intensity as you approach the third left interspace, where it is heard most distinctly. Is not transmitted to the left axilla and is not affected by posture.

The abdomen is slightly protuberant and gives the impression of visceroptosis. The liver is palpated two fingerbreadths below the costal border. Spleen is not felt.

The genitals are negative except for the presence of a rather long prepuce.

The upper extremities are negative. The tibiae of both lower extremities are prominent. Two cm. behind the external malleolus of left foot is a shallow ulcer about 1 cm. in diameter. Just inferior to the internal malleolus of the right foot there is a similar ulcer 3 cm. in diameter. There is no limitation of motion in the joints.

*Laboratory Findings*—Blood-picture. Erythrocytes per c mm, 2,200,000. Hemoglobin (Tallqvist), 40 per cent. Color index, 1.00. Leukocytes per c mm, 21,000. Small mononuclears, 20. Large mononuclears, 0. Polymorphonuclear neutrophils, 75. Eosinophils, 5. Basophils, 0.



Fig. 215—Photomicrograph of blood from case of sickle-cell anemia.

Practically all the erythrocytes are in elliptic or sickle shapes. Polychromasia marked. (See Fig. 215.) No basophilic stippling. Fifteen normoblasts and microcytes noted while counting 100 leukocytes.

Blood Wassermann (original and Bass-John) negative.

Bilirubin (van den Bergh). Reading of 10 units in the indirect reaction.

Blood chemistry. Total non-protein nitrogen, 37.5 mg. per 100 c.c. Urea nitrogen, 20 mg. per 100 c.c. Creatinin, 1.8 mg. per 100 c.c.

Fragility test. Beginning hemolysis at 0.32 per cent sodium chlorid and complete hemolysis at 0.22 per cent.

Renal function (phenolsulphonephthalein) 50 per cent after two hours.

Sputum. Several examinations failed to reveal the presence of acid fast bacilli.

Feces. No intestinal parasites or ova found. Negative for occult blood.

Urine. The color was of a deep amber, specific gravity 1.008, reaction acid, albumin negative, sugar negative, indican negative, acetone and diacetic acid negative. The Gmelin test for bile was negative. Under the microscope

no casts were found Only a few epithelial cells and an occasional pus-cell were present

Roentgen ray of chest Postero-anterior view of the chest shows hilar shadows exaggerated Hazy, faintly mottled infiltration radiating from the upper hilar zone on the right side, probably pulmonary tuberculosis

Discussion —From the findings in this case and from others in the literature we see that sickle-cell anemia is a disease characterized by (1) The peculiar, bizarre, crescent-shaped erythrocytes, (2) the fact that it seems confined practically to the negro race, and (3) is hereditary

Sydenstricker states that his series included ten family groups, and in every instance where it was possible to examine the blood of relatives a similar incidence was found

Otherwise the picture is very much that of a primary anemia and, as one has shown, also in a great measure that of familial hemolytic icterus

In the active cases the symptoms are weakness, fatigue, dyspnea, and palpitation These are always present. Muscle and joint pains occur at frequent intervals There are frequent attacks of nausea and vomiting, associated with epigastric and left hypochondriac pains, though in this case they were not present. A low-grade fever is generally found Leg ulcers are nearly always present. They are prettily demonstrated in this patient.

The physical signs are striking The patient is poorly nourished with marked signs of retarded development The sclerae present a greenish yellow, which varies with the individual case The mucous membranes are pale, the tongue markedly pallid There is more or less general lymphadenoid hyperplasia The heart shows the changes commonly associated with anemia The lungs are generally negative The liver is constantly enlarged and the spleen is never felt, except in the presence of malaria The legs show ulcers or scars and often some edema

The urine always shows a low specific gravity, with usually traces of albumin and urobilin in small amounts In this patient neither albumin nor urobilin were present.

The stools show nothing of importance The gastric acidity is generally decreased



This patient's blood shows the usual red cell sickling with about the average total count and hemoglobin estimation. Several observers have found that the sickling markedly increases in a sealed cover-slip preparation. No megaloblasts were found. Basophilic stippling is said to be rare. The increased leukocyte count is always present in these cases, the count ranging from 20,000 to as high as 60,000. Several observers have found phagocytized erythrocytes in large mononuclear cells, but in this case I was not able to demonstrate this phenomenon. The serum is of a deep yellow color and contains large amounts of bilirubin. In this instance the indirect van den Bergh reading was 10, or about twenty times the amount found in normal serum. The resistance of the erythrocytes in hypotonic salt solutions is increased.

An effort was made to see if the cause of the sickling lay in the red cell itself or in the serum. Normal erythrocytes were placed in a patient's serum and the patient's cells in normal serum. It was found that the normal cells were not affected in the patient's serum and that his cells remained sickled in normal serum. So the cause seems to reside in the stroma of the cell itself.

**Pathogenesis** —The condition is probably a familial and hereditary defect of the spleen and the blood-forming organs, with a resulting change in erythrocytes which predisposes to hemolysis and phagocytosis. The anemia is the result of excessive blood destruction, activated by factors that would be innocuous in a normal person. The increased indirect van den Bergh reading that is present supports this view of a hemolytic process.

In histologic studies the spleen appears packed with red blood-cells, more in the spaces of the pulp than in the sinuses. Fibrosis is also present and large focal deposits of iron-free pigment. The elastic tissues of many of the splenic arterioles gives the iron reaction. Pigment is also present in excess in the liver both in the hepatic and Kupfer cells, and can always be found in the endothelium of the capillaries of various organs, in the collecting tubules of the kidneys and in the glomeruli as well. The destruction of red blood-cells is most pronounced in the

spleen No iron pigment is found in the bone-marrow. Just what the toxin is we do not know

*Treatment*—The treatment of these cases, as in the primary anemias in general, is notoriously unsatisfactory. Various things have been tried, mainly iron and arsenical preparations, rest in bed, plenty of fresh air and sunshine, and frequent small transfusions of blood, the latter probably being of more use than anything else tried

*Prognosis*—The outlook is bad, the course being gradually a downward one, and the curtain is generally rung down by an intercurrent disease It has been stated that these cases rarely live beyond the age of thirty years

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### QUINIDIN IN THE TREATMENT OF AURICULAR FIBRILLATION

"THE action of quinidin upon auricular fibrillation has now been widely yet (when it's importance is considered) by no means sufficiently investigated. Since its introduction in 1918 numerous reports have appeared abroad giving the results in cases now numbering hundreds." Perhaps this great enthusiasm on the part of the internist in the use of quinidin in these cases of auricular fibrillation was to be expected because of the intense dramatic changes induced in the cardiac mechanism by this drug. However, the advisability of a general use of this new remedy in this most interesting of heart affections is still undetermined, though its beneficial effect in some cases is beyond question.

It is my intention to discuss briefly the advisability of its general use and, besides, to give to the reader, in a concise manner, the general beliefs of the nature of auricular fibrillation and the conclusions drawn as to the benefits derived from quinidin therapeutics in this condition.

**Historical**—Although quinidin as a drug had been known for many years, our knowledge of its real action on the fibrillating heart dates back to the description furnished us by Frey, published for the first time in 1918. "Following a clue from Wenckebach, Frey made an extensive study of the effects of various cinchona derivatives on the cardiac mechanism of laboratory animals, principally the dog. After much experimentation he found, that of all the cinchona derivatives, quinidin had a most efficient action in restoring to normal rhythm a heart that had previously been irregular.

Following the lead of Frey many workers have since investigated and studied the action of quinidin. We might briefly summarize the results of all this work by saying that Frey's findings have been completely corroborated. Among the most influential workers in this field might be mentioned Lewis<sup>2</sup> and his co-workers,<sup>3</sup> Mackenzie,<sup>4</sup> Clark-Kennedy,<sup>5</sup> John Hay,<sup>6</sup> H. M. Korns,<sup>7</sup> Viko, Marvin, and White.<sup>8</sup>

Notwithstanding the fact that much study, both experimental and clinical, has been done with quinidin, its employment in cases of auricular fibrillation has been done with a great deal of hesitancy in many of our best American clinics. Perhaps this might be attributed to the fact that digitalis has stood the test of many years and is in a large number of cases entirely adequate. On the other hand, the explanation might be found in the fact that undue stress has been laid by some writers with clinical experience with the drug upon the small percentage of fatalities that have occurred during its administration, a percentage apparently no greater than that which occurs in any unselected series of cases of auricular fibrillation irrespective of treatment.

**Nature of Auricular Fibrillation**—Before entering further into the discussion of quinidin and its action perhaps it would be well to stop here and briefly consider the nature of auricular fibrillation. This cannot be better explained than in the excellent description given by Emanuel,<sup>9</sup> which is as follows: "Auricular fibrillation is a functional disorder of rhythm arising in a heart that was previously contracting with an orderly regular rhythm known as sinus rhythm. Normally the healthy adult heart contracts some 70 to 80 times per minute, in response to impulses generated and discharged at a regular rate. These impulses arise in the pace-maker of the heart—the sino-auricular node, a small collection of fibrous tissue in which are numerous specialized muscle-fibers, some nerve-cells, and some nerve-fibers, it is situated in the right auricle, near the opening of the superior vena cava, and the vagal and sympathetic nerve trunks are connected with it. When auricular fibrillation occurs the function of the pace-maker remains in abeyance, and its rôle

is taken up by the muscle-fibers of the auricular walls. These fibers have heretofore only been accustomed to conduct impulses from the pace-maker to the ventricles. With the onset of auricular fibrillation they assume a new function and generate some 400, 500, or 600 impulses per minute.

"In auricular fibrillation, then, these impulses replace the 70 to 80 impulses formerly generated by the specialized fibers of the pace-maker, they are conveyed by the auriculoventricular bundle to the ventricles, which cannot respond to so large a number of impulses, but do respond to many of them, albeit in a disorderly fashion, thus the ventricular contractions follow one another at irregular intervals and are of varying force. Consequently, when auricular fibrillation occurs, a pulse previously regular in force and rhythm becomes totally irregular in both respects, becomes, in fact, the characteristic and generally rapid pulse of auricular fibrillation."

**Action of Quinidin on Fibrillating Auricle**—Having considered the mechanism of auricular fibrillation, we will now briefly consider the mode of action of quinidin in this condition. Much has been written on this subject by many authors. Many theories have been evolved explaining this action, but most of these have failed of recognition and acceptance because their falseness was proved by laboratory experimentation.

Of all the theories advanced in explanation of this phenomenon, the one by Lewis<sup>2</sup> and his co-workers,<sup>3</sup> notably Drury and Ilescu, and Wedd, has found most general acceptance. According to this theory the effect of quinidin upon the fibrillating auricle may be stated as follows: "That it brings about a lengthening of the refractory period in the auricle, that it slows conduction in the auricle, that it has a paralyzing action upon the vagi, and that it has a direct action upon the junctional tissues." Up till the present time no definite experimental evidence has been advanced to disprove these conclusions. On the other hand, the above findings have been substantiated by the experimental work of many investigators. Foremost among these latter might be mentioned Korns,<sup>7</sup> who published in 1922 a most complete report of the results of very careful experimenta-

tion upon the dog's and the guinea-pig's heart, together with a report of his vast clinical experience with quinidin

**The Routine Use of Quinidin Proper Selection of Cases Indications and Contraindications**—From the statements made in the foregoing paragraphs in regard to the action of quinidin upon the fibrillating heart, it would appear that its routine use in any or all cases would be proper. Such was the opinion arrived at by practically the entire medical profession following the first reports of Frey and his successors, and, as is usually the case when a new drug is employed by many not wholly informed as to its physiology and pharmacology and inexperienced in its proper use, it was not very long before reports of failures and fatalities filled the literature. This decision in favor of its general use has since been contradicted by the sad experiences of many who made it only too hastily and unwisely, and it is to be said most emphatically that it should not be routinely employed in treating every person suffering from auricular fibrillation.

Korns<sup>10</sup> in 1922 was one of the first to warn us that the indications for the use of quinidin and digitalis were entirely separate and clearly defined. Writing of his clinical experience with the drug, Levy<sup>11</sup> states, "that in only about 50 per cent of unselected cases" is it possible to restore normal rhythm. Likewise Fraser<sup>12</sup> adds a most emphatic note of warning of the "unpleasant and dangerous" effects capable of being produced by quinidin if employed haphazardly. And so it goes throughout all that has been written on this subject, no matter in what language, this warning against its general use. We might go further and make the statement, and feel that we are entirely correct, that practically all authorities are agreed on this one phase of the subject.

Since quinidin has its proper place in the therapeutics of auricular fibrillation, our next step, then, is to consider when and under what circumstances should the drug be used. In other words, our problem now is that of proper selection of cases for quinidin therapy. The solution of this problem is not an easy matter and is made more difficult because it takes into con-

sideration the personal equation. Although indications and contraindications for the use of quinidin have, on the whole, been worked out, still the final decision as to its use depends on the individual clinician and his ability to discover present in each case those physical signs which either indicate or contraindicate its use.

As stated before, it is most difficult to choose any number of cases of auricular fibrillation in which a brilliant therapeutic effect may be anticipated. However, it is much less difficult to exclude those cases showing other signs, the presence of which, experience has shown, makes success with quinidin therapy unlikely.

Various criteria have been advanced for the selection of those cases most likely to be benefited by quinidin. The following are the chief ones universally agreed upon by the best authorities:

- 1 Cases which show the presence of a good myocardium that is with little or no cardiac hypertrophy
- 2 Cases which show little or no signs of heart failure, or in which the symptoms of heart failure clear up promptly after treatment is instituted
- 3 Cases wherein the fibrillation is of recent onset and especially if of short duration
- 4 Cases which show no serious valvular damage to the heart

Besides the above indications, it has been clearly shown that quinidin is of little value in restoring to normal rhythm those cases of auricular fibrillation of thyrotoxic origin, as in hyperthyroidism unless the active thyrotoxic factor is first treated and eliminated.

Likewise in cases where the causative factor of the fibrillation is a somewhat similar active agent, as in rheumatism and in rare cases of malaria, this causative agent must be first done away with before we can expect any stable action from the use of quinidin.

In explaining his method of selection of cases Emanuel<sup>9</sup> writes as follows: "In selecting cases for quinidin therapy I have based my selection entirely on the response of the patient



to digitalis Given a case suffering from cardiac failure with auricular fibrillation, the patient is treated in the routine manner by rest and digitals, with purgatives, etc If (as in the vast majority of cases) the patient responds well to treatment, we may deduce that auricular fibrillation is the cause of the heart failure, in these cases quinidin should be used, for if we can change the rhythm we cure the heart failure If, however, there is no satisfactory improvement in the patient's state in spite of the lowering of the ventricular rate to within normal limits, then the cardiac failure is due not to auricular fibrillation, but to a worn-out heart muscle This only occurs in a small number of cases, and in these quinidin should not be used

White is of the opinion that any chronic fibrillation of one year or more standing is a contraindication to the use of quinidin, because

- 1 Any return to normal rhythm is of short duration
- 2 The danger of embolism, arising from a clot formed in the auricle during fibrillation, is increased
- 3 Respiratory paralysis more likely
- 4 Sudden death<sup>13</sup> has resulted, the cause of which is unknown, but possibly due to ventricular fibrillation

**Method of Treatment. Mode of Administration. Dosage—**Following the introduction of quinidin many clinicians began to disagree with the method of treatment and dosage recommended by Frey in his early articles, so that after a time there were many conflicting beliefs as to the best methods and dosage to be employed However, after much clinical observation, most of these difficulties have been eliminated, and at the present time there is a more or less general plan of treatment usually pursued A great deal of credit for this is due the English school of clinicians, and especially those groups of workers headed by Lewis and Mackenzie

To explain the general plan of treatment usually adopted Parkinson and Nicholl are quoted "The sulphate of quinidin is used and given as a powder in gelatin capsules, each containing 5 grains Preliminary doses of 5 and 10 grains were given on the first and second day of treatment respectively, lest there

should be any idiosyncrasy toward the drug. It was then increased to 15, 20, 30, and 40 grains daily until the change in rhythm (if any) occurred. The daily amount was given in divided doses—*e g.*, 30 gr. as 10 gr. three times a day. When normal rhythm was restored the dose was gradually reduced until 5 grains were taken twice or thrice daily.”

**Dangerous Effects of Drug**—It must always be borne in mind that quinidin is not a cardiac tonic, but rather a cardiac poison, therefore when it is used the patient should be watched carefully for any signs or symptoms of the toxic effect of the drug. Briefly these toxic symptoms are headache, dizziness, nausea, vomiting, and urticarial rash. Further, it should be remembered that unwise use of the drug in dosage higher than already advised is dangerous and might easily end in sudden death of the patient. Likewise tendency to embolism is more likely to occur with the use of quinidin, and therefore any case giving a history of previous occurrence of embolus or any case which is of long duration should better not be treated with quinidin.

**Discussion**—In reviewing the literature one is forcibly impressed with the fact that all of the recognized authorities in cardiology stress the futility and danger of trying to supplant digitalis by the use of a comparatively new drug like quinidin. Viko, Marvin, and White<sup>8</sup> were one of the first to take note of this fact, and they employed quinidin in combination with digitalis, with most excellent results. Since then all authorities have recognized and have recommended the supplementation of digitalis therapy with the use of quinidin in those cases of auricular fibrillation in which there are no contraindications to the use of the latter.

Another important fact, often disregarded, is that there are limitations to the use of quinidin, and unless these are respected the chances of success in the use of the drug are necessarily much less than if they are recognized and kept in mind. Therefore quinidin should not be regarded as a drug for treating symptoms of cardiac failure, but merely a drug for altering an abnormal rhythm. Likewise it must be remembered that whereas quinidin

is capable of restoring sinus rhythm in auricular fibrillation, it cannot prevent its recurrence. Therefore its use in any case depends entirely upon the liability of the fibrillation to recur. Because of our lack of knowledge at the present time this liability cannot be estimated.

**Conclusions**—1 Quinidin is capable of restoring normal sinus rhythm in properly selected cases of auricular fibrillation, especially if the cause can be successfully treated or has ceased to be active.

2 Cases of auricular fibrillation which show evidence of cardiac hypertrophy or in which there are extensive valvular lesions are not suitable for quinidin treatment.

3 It should be borne in mind always that quinidin is a very toxic drug and its use by inexperienced clinicians fraught with dangers, and perhaps death, to the patient.

4 The use of quinidin in suitable cases of auricular fibrillation should be confined to supplementing the digitalis treatment and not in supplanting it.

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# CLINIC OF DR MORELL W MILLER

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### THE NATURE AND TREATMENT OF THE LEUKEMIAS

SINCE October, 1845, when Hughes Bennett, of Edmborough, first described to the medical profession a case of "suppuration of the blood with enlargement of the spleen and liver," which he termed "leukocy themia," has leukemia been an interesting and baffling study

Many and ingenious devices have been contrived to combat this fateful malady. Modern concepts have torn down and discarded the older theories regarding the leukemias, but the fundamental knowledge of these blood dyscrasias is still lacking. Numerous and varied are the theories of leukemia and widely divergent are the methods of its treatment. During the past two decades, however, certain findings have been definitely established which throw considerable light on the nature of the leukemic process.

To understand clearly the most recent developments in the study of this malady and to realize the departure from the original meaning it may be wise to recapitulate the outstanding features in the history of the pathology and treatment of this interesting disease phenomenon. The object of this paper becomes, then, to follow in outline the developments in the pathology of this disease, to touch lightly upon its etiology and modern methods of treatment, and to show its present unsettled state.

Virchow in November, 1845 first identified the disease as a specific disease of the blood-forming organs, and considered the white cells contained in the blood as identical with those recovered from wounds, *i. e.*, pus-cells, and named the disease "leukemia." He believed the pathognomonic factor was merely

ance of considerable work from the fields of anatomy, especially by Maximow and Sabin, showing that the hemopoietic system is scattered, potentially at least, throughout the whole body and especially in the connective tissue about blood-vessels, added considerable weight to this theory, which until quite recently stood unchallenged as the working basis of present-day classifications of the blood dyscrasias. That its service as a nucleus upon which to build present-day knowledge has been amply made use of is attested by its many modifications.<sup>1</sup>

Status lymphaticus and lymphogranulomatosis were the first additions within this category to be added to the tabulation. Then a new group of lymphomas and a systematic lymphosarcomatosis<sup>2</sup> was added. Others<sup>3</sup> would include such skin conditions as mycosis fungoides for reason of a certain amount of pathologic and clinical similarity. Ward<sup>4</sup> suggests that in addition to this classification the leukemias be considered as primary when no contributing causal factor is discernible, and all other leukemias as of secondary type.

Such is our present understanding, in which leukemias are considered as consisting of several states rather than a single disease picture, and so has been termed "leukemic states."

It is obvious that throughout these vicissitudes of scientific progress the term "leukemia" (white blood) fails to meet all the requirements that science demands of it, since in reality the blood findings are of only secondary significance. Believing the term "leukemia" entirely inadequate, Waugh has advanced a new classification<sup>5</sup> with a new nomenclature. He believes that the

<sup>1</sup> MacCallum, *A Text-book of Pathology*, 2d ed., W. B. Saunders, Phila., 1923, p. 828.

<sup>2</sup> Kodama, T., *Lymphatic Leukemia—Primary Disease of Lymphatic Issue*, Mitt. d. med. Fakult. d. Univ. zu Tokyo, ab Jour. Amer. Med. Assoc., 1923, 81, 1156.

<sup>3</sup> McGlasson, I. I., and Ichmann, O. F., *Comparative Observations on Skin Manifestations of Leukemias and Allied Conditions*, Texas State Jour. Med., 1921, 20, 177.

<sup>4</sup> Ward, F. R., *The Leukemias*, Proc. Roy. Soc. Med., Med. Sect., 1913, 7, 126.

<sup>5</sup> Waugh, J. R., *The Nature and Classification of the Leukemias*, The Canadian Med. Jour. and Rec., 1925, 15, 153.

various pathologic processes of the hemopoietic tissues which are of a progressive leukoplastic nature fall naturally into four groups, namely.

- 1 Hyperplasias
- 2 Kataplasias
- 3 Dysplasias
- 4 Neoplasias

Each group is further divided histologically into lymphoid or myeloid subgroups according to the branch of the system affected. According to the organ affected it may be lymphadenic, lienal, or medullary, to the blood-picture, aleukemic, leukemic, or subleukemic, to pigmentation achloromic or chloromic, and to clinical nature, acute, subacute, or chronic.

By "hyperplasia" is understood a process characterized by an increase in cell elements which are essentially the same in character as the normal. In this condition the controlling mechanism of leukopoiesis, although seriously interfered with, is not irreparably damaged.

The kataplasias include what is now known as the leukemias and consist of a generalized systemic overproduction of cells which are of an immature and embryonic character. When this overproduction is on the lymphoid side it is a lymphosis, when on the myeloid side it is a myelosis. If the overproduction tends to remain localized, the tumor mass is described as a hyperplastic lymphosis, or myelosis, but if there is, on the other hand, much infiltration and replacement it is sarcoïd.

By dysplasias are meant those systemic processes which have become so perverted and altered from the normal leukopoiesis as to be hardly recognizable as such, the controlling mechanism is not here disturbed, but the hemopoietic tissues themselves undergo progressive alteration. The neoplasias consist of a local emancipation of cells, which, in turn, undergo embryonic proliferation in some spot removed from the original focus.

It is claimed that this classification permits of a broader and truer conception of the so-called leukemias. Whether or not it will meet with general acceptance and withstand the test of time remains for the future to tell. Although in a measure artificial this classification seems logical.

Szilard<sup>1</sup> believes the seat of the pathologic process to be in the circulating cells which have an increased fragility. The increased fragility permits of rapid cell destruction, this throws an increased demand upon the leukopoietic tissues, which, in turn, undergo compensatory hypertrophy and hyperfunction, thus giving rise to the characteristic tissue appearance.

Of the etiology of the leukemias little is known. The etiology has been variously ascribed as being due to nervous influence, protein disintegration, endocrine dysfunction, toxic conditions, specific infections, and new growths of the leukopoietic tissues. Much can be said against and but little in favor of most of these theories. Certain pathologists<sup>2</sup> consider that the leukemias are new growths of the blood-forming organs, but the pendulum of popular opinion seems to swing in the direction of the specific infection theory.<sup>3</sup> Various observers<sup>4</sup> believe it to be a transmissible infection, and others<sup>5</sup> claim to have isolated the causative organism. These findings are in keeping with the clinical observation that frequently leukemia<sup>6</sup> or leukemic-like reactions<sup>7</sup> occur with or in association with septic processes in the body.

Heredity, race, age, sex, trauma, altitude, and mental and physical states are advanced as factors in the development of leukemia. The relation to pregnancy is interesting, conception

<sup>1</sup> Szilard, Aleukemic Myeloses, *Deutsch Arch f Klin Med*, 1924, 144, ab *Jour Amer Med Assoc.*, 1924, 83, 649

<sup>2</sup> MacCallum, W G, *A Text-book of Pathology*, 2d ed, W B Saunders, Phila, 1920, p 827

<sup>3</sup> Ward, F, *The Infective Theory of Acute Leukemia*, *Brit Jour Child Dis*, 1917, 14, 10

<sup>4</sup> Sellards, A W, and Baetjer, E A, *The Clinical Significance of the Irregular Distribution of Various Cells and Parasites in the Blood stream and the Production of Abortive Leukemic Changes and of Splenomegaly in the Macacus Rhesus*, *Bull Johns Hopkins Hosp*, 1918, 29, 135

<sup>5</sup> Inaba, I, and Ohoski, S, *A New Microbody Found in the Blood in Case of Myelogenous Leukemia and the Efficacy of Arsphenamin on the Disease*, *Amer Jour Dis Child*, 1918, 16, 1

<sup>6</sup> Greene, C L, *The Leukemias*, *Practice of Medicine*, Tice, W F Prior Co, Hagerstown, Md, vol 6, 833

<sup>7</sup> Musser, J H, Jr, *Unusual Types of Leukemia*, *Medical Clinics of North America*, 1923, 6, 939

is rare during the course of the disease. The disease may begin during pregnancy and progress rapidly to a fatal termination.

Leukemia has a wide distribution in the animal kingdom. In the spontaneous form it is frequently found in the common fowl, to a lesser extent in the dog, swine, and mice, and but rarely in the ox. Experimental forms have been produced with relative ease in a considerably wider range of animals, and in the continuation of these investigations much important data will doubtless be forthcoming.

In human beings leukemia shows a marked preference for the male sex, the incidence<sup>1</sup> for all leukemias being in round numbers 3/1. Each of the three forms of leukemia has a definite age of election.<sup>2</sup>

The majority of cases of chronic myelogenous leukemia occur between the ages of twenty-five and forty-five years. Chronic lymphatic leukemia occurs later and shows its majority of cases between the ages of forty-five and sixty. In acute leukemia, on the other hand, there is a decided preference for ages below twenty-five, and in this period the maximum incidence is the first five years, falling sharply in the next five, but rising to the second maximum between the years of fifteen and twenty.

The incidence of leukemia in children is considerably higher than was formerly believed. Myeloid leukemia is rare before the sixth year, but there are several carefully studied cases of myelogenous leukemia in infants. Knox describes a case of acute myelogenous leukemia in a nine-month infant, and Pisek<sup>3</sup> reports the same condition in an infant fourteen months of age. Opitz<sup>4</sup> recently reports a case of acute myelogenous leukemia in

<sup>1</sup> Minot, Buckman, and Isaacs, Chronic Myelogenous Leukemia, Age Incidence, Duration, and Benefit Derived from Irradiation, Jour. Amer. Med. Assoc., 1924, 82, 1489.

<sup>2</sup> Ward, G., The Infective Theory of Acute Leukemia, Brit. Jour. Child Dis., 1917, 14, 20.

<sup>3</sup> Pisek, G. R., Acute Myelogenous Leukemia in an Infant, Arch. Pediat., 1916, 28, 938.

<sup>4</sup> Opitz, J., Acute Myelosis in Infants, Med. Klin., 1924, 20, 891, ab Jour. Amer. Med. Assoc., 1924, 83, 568.



a three-month infant, which is seemingly the youngest case on record

Although the leukemic condition shows a sharp fall in incidence after the age of sixty, occasional cases have been reported in elderly people Pinelis reports a case of acute leukemia in a man seventy-three years old, and Ordway and Gorham have observed chronic myelogenous leukemia in a woman seventy-five years old

The therapeutic measures in use for the treatment of leukemia were largely symptomatic and directed against the associated anemia until relatively recent years, when it was discovered empirically that certain agents have a more or less specific effect in reducing the greatly increased number of white blood-cells Modern treatment, therefore, is directed not only toward the associated anemia, but toward the leukemia itself

Drugs used in treating the anemia are arsenic in the form of Fowler's solution, cacodylate of soda or of iron, and the arsphenamin preparations The injection of whole, defibrinated or citrated blood, iron in its various forms, red bone-marrow, and colloidal metals have been advocated

Of the measures directed toward the destruction of the increased white blood-cells, benzol, splenectomy, Roentgen ray, radium, thorium, and various other radio-active preparations have been used to induce remissions in the chronic type of the disease The acute form is apparently not influenced by any treatment Both the lymphatic and myelogenous forms respond alike to whatever form of treatment is directed against them

Santassen in 1897 first noticed the reduction of the total leukocyte count, with a corresponding reduction of reds in the circulation of persons using benzol in a bicycle factory In 1910 it was confirmed by Selling<sup>1</sup> that benzol has a leukotoxic action This action suggested its use in leukemia, and Koranyi made its first practical application in 1912, with a marked reduction in the blood-picture The reports of sudden death to patients

<sup>1</sup> Selling, L., A Preliminary Report of Some Cases of Purpura Hæmorrhagica Due to Benzol Poisoning, Bull Johns Hopkins Hosp, 1910, 21, 33

using it, its marked toxic effect, and the disagreeable symptoms arising from its administration preclude its use in general practice, except in the absence of radium or Roentgen ray. Its greatest field of usefulness lies with the chronic myeloid form. Recently benzylbenzoate,<sup>1</sup> a benzol derivative, with much less toxicity than benzol, has been suggested in the treatment of these cases.

Splenectomy was first performed by Bryant in 1866. The mortality rate is tremendous if the splenectomy is performed during a period of splenomegaly. Treatment of leukemia by splenectomy<sup>2</sup> in conjunction with irradiation has been reported successful at the Mayo Clinic.

Roentgen-ray therapy was first practised in the management of leukemia by Senn in 1903. The emanations have a clearly useful field of action in the treatment of the leukemias. Absolute cure cannot be obtained, but decided remissions with temporary improvement occur. Irradiation<sup>3</sup> has no detectable effect on prolonging the duration of either form of the disease, but irradiation properly administered undoubtedly benefits symptomatically patients with the chronic form, and the chronic myelogenous more than the chronic lymphatic. McAlpin and Sanger<sup>4</sup> in a recent survey of a number of cases verify these findings, and further show the basal metabolism and hemoglobin content of the blood to be reliable prognostic means.

Renon, Degrais, and associates made application of radium over the spleen in cases of leukemia as early as 1910, with beneficial results. Since then numerous cases have been reported, and in particular by the French authors, with beneficial results.

<sup>1</sup> Haughwout, F. G., *Lymphatic Leukemia*, New York Med. Jour., 1919, 110, 180.

<sup>2</sup> Giffin, H. Z., *Splenectomy Following Radium Treatment for Myelocytic Leukemia*, Med. Rec., 1918, 94, 1020.

<sup>3</sup> Minot, G. B., and Isaacs, R., *Lymphatic Leukemia, Age Incidence, Duration, and Benefit Derived from Irradiation*, Boston Med. and Surg. Jour., 1924, 190, 1.

<sup>4</sup> McAlpin, K. R., and Sanger, B. K., *Blood Counts and Basal Metabolism of Leukemias Under Roentgen Ray Treatment*, Amer. Jour. Med. Sci., 1924, 167, 29.

Ordway<sup>1</sup> reports a case resistant to both Roentgen ray and benzol completely amenable to radium, and suggests alternating doses of radium, Roentgen rays, and benzol. Giffin<sup>2</sup> has observed favorable remissions with a seeming increase in the length of life. A summary of 25 cases<sup>3</sup> seems to indicate radium to be of value in all chronic cases, but to be used with caution, if at all, in acute cases. Irwin<sup>4</sup> reports the results of radium therapy to be more certain and with a tendency to longer remissions than Roentgen ray.

Of the radio-active salts, thorium X entertains a considerable amount of popularity at present for reason of the relative ease in obtaining accurate dosage. Considerable symptomatic improvement has been noted in all cases under treatment in the Paris Hospital up to the present writing. Marked improvement in the symptomatology and the associated anemia, together with lengthening of life, is also said to occur.

In recapitulation, the following inferences may be drawn.

(1) The occurrence of embryonic leukocytes in the bloodstream is the pathognomonic factor of leukemia.

(2) The leukemias are generalized affections manifesting themselves by clinically involving one type of white cell.

(3) The etiology of the leukemias is unknown.

(4) The association of the leukemias with specific infections and their experimental transmission in laboratory animals favors the infective theory.

(5) The incidence of leukemia is three times greater in males than in females, and each type of leukemia has definite age periods.

<sup>1</sup> Ordway, T, Remissions in Leukemia Produced by Radium in Cases Completely Resistant to Roentgen Ray and Benzol Treatment, *Boston Med and Surg Jour*, 1917, 176, 490.

<sup>2</sup> Giffin, H Z, Observations on the Treatment of Myelocytic Leukemia by Radium, *Boston Med and Surg Jour*, 1917, 177, 686.

<sup>3</sup> Scheiner, B G, and Maltick, W L, Radiation Therapy in Treatment of Leukemias Summarized from a Series of 25 Cases, *Amer Jour Roentgen*, 1924, 12, 126.

<sup>4</sup> Irvin, E L, Leukemia, with Observations in the Treatment and Findings, *New Orleans Med and Surg Jour*, 1923, 75, 367.

(6) The present classification of leukemias unsuccessfully endeavors to restrain a dynamic disease process within circumspect boundaries, and the recently suggested classification permits of a broader understanding of the leukemic process than does the classification now in use

(7) Roentgen ray, radium, and some radio-active salts relieve symptoms and promote a sense of well-being, but do not appreciably lengthen the duration of life or cure the disease



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### LIVER FUNCTION AND LIVER FUNCTION TESTING

IN the last few years considerable work has been done on functional tests of the liver. Recently Rosenthal<sup>1</sup> has introduced a new method based on the ability of the liver to remove phenoltetrachlorophthalein from the blood-stream in a given length of time. This test has more or less supplanted other liver function tests, or at least it can be taken as a standard of comparison for the other tests.

The selection for the best method for determining liver and biliary tract function is at present an important problem, as testified to by current medical literature. It is my purpose to consider the various ways and means of determining liver function and endeavor to arrive at some definite conclusion as to the respective value of the various functional tests of this organ.

It is thought that through functional procedures and following the development of refined methods for studying liver function much progress will be made as to diagnosing, treating, and estimating the amount of liver pathology fairly early in the disease, and also to study the course of a disease and to tell the benefit derived from therapeutic measures directed toward the cure of the condition present demanding attention.

The liver is the largest single organ in the body and one of the most important, as its function is not only necessary for a condition of health, but for a continuation of life itself. Dr William J Mayo,<sup>2</sup> on speaking of the vital importance of liver function, says

"The liver was recognized even by ancients as the king of organs, standing as a buffer, on the one hand, between the general circulatory system and the gastro-intestinal tract, and, on the other hand, between the general circulation and the

spleen, which filters from the blood micro-organisms and toxins that it is unable to destroy, sending them to the liver through the portal circulation for destruction and detoxication. The liver detoxicates chemical poisons, such as chloroform, phosphorous, and arsenic, as well as biochemical poisons produced within the body. Yet for many reasons we know little concerning the functions of early pathologic conditions of the liver. Its concealed situation prevents us from accurate means from without of early diagnosis. Its power to regenerate injured cells is not equaled by any other organ of the body, and its enormous margin of safety prevents us from knowing just what is taking place in the earlier stages of hepatic diseases, and the appalling nature of the pathologic changes when they are sufficient to enable physical demonstration has made the liver an organ of mystery and conjecture. I venture to predict that the next few years will bring forth productive research demonstrating that the causes of many of the changes in the so-called vital organs which lead to death do not primarily originate in the nervous system, heart, lungs, or kidneys, but are the result of hepatic insufficient purification of the blood, thus making possible much sound prophylaxis.

"The functions of the liver are (1) Defense against invasion of the body by micro-organisms and the detoxication of the toxic products brought to the liver by the portal circulation, (2) fat metabolism, (3) protein metabolism, (4) carbohydrate metabolism, and (5) bile function."

Howell<sup>2</sup> says, in speaking of the liver

"Its functions are manifold, but in the long run they depend upon the properties of the liver cells which constitute the anatomic and physiologic unit of the organ, although there is histologic evidence that some of the endothelial cells of the capillaries of the liver have marked phagocytic properties, and it is possible that their activity may play a contributory part in some of the functions of the liver, for example, in the destruction of the red corpuscles that precedes the formation of bile-pigments. The liver cells are seemingly uniform in structure throughout the whole substance of the liver. The physi-

ology of the liver cells falls naturally into two parts—one treating of the formation, composition, and physiologic significance of bile, and the other dealing with the metabolic changes produced in the mixed blood of the portal vein and the hepatic artery as it flows through the lobules. In this latter division the main phenomena to be studied are the function of urea and the formation and significance of glycogen, but it cannot be doubted that the liver possesses other important metabolic functions which at present are imperfectly understood, such, for example, as its relation of fibrinogen and antithrombin.”

Boucart speaks of puerperal infection and insufficiency of the liver. He considers the liver of vast importance in combating infection, and says that liver function lags because of inadequate blood supply.

Hess,<sup>3</sup> abroad, and Napoleon, of Boston, emphasize the protecting rôle played by the liver in a decompensating heart by taking up a large amount of blood during venous engorgement.

Mann and Magath,<sup>4</sup> of the Mayo Foundation, have studied the effect of total liver extirpation, and also the effect of pancreatectomy along with the liver function in relation to the carbohydrate metabolism.

H. Rogers speaks of function of glycogen and the value of carbohydrate in operative cases.

**Tests**—Phenoltetrachlorphthalein. The tests for liver function are almost as numerous as the drugs that have been used in the treatment of tuberculosis. These tests are directed at the various liver functions and then run on into the purely arbitrary tests for dye excretion. Various dyes have been used, such as azorubin S, methylene-blue, indigocarmin, rose bengal, Congo red, phenoltetrachlorphthalein, and bromsulphthalein, but the one most experimented with in this country has been phenoltetrachlorphthalein. It was studied by Abel and Rowntree<sup>5</sup> in 1909 as a subcutaneous purgative.

The most valuable accurate method of measuring the functional integrity of the liver are those based on the ability of the liver to withdraw phenoltetrachlorphthalein from the bloodstream after intravenous injection. It has been said that as



phenolsulphonephthalein, a water-soluble product, is excreted by the kidneys, so phenoltetrachlorophthalein, a fat-soluble substance, is excreted by the liver<sup>6</sup> Excretion depends on two factors open drainage and a normal secreting cell

There are several different methods that have been tried in regard to this one dye (phenoltetrachlorophthalein), but before discussing those we will consider a brief history of liver function tests with this dye

In 1909 Abel and Rowntree<sup>5</sup> determined that phenoltetrachlorophthalein is excreted almost entirely by the liver and when injected intravenously is non-toxic Rowntree, Hurwitz, and Bloomfield,<sup>7</sup> and Whipple, Mason, and Pughthal<sup>8</sup> in 1913 conducted experiments showing that the dye could be recovered in the stools and that the excretion was in proportion to the amount of liver pathology This method was later found to be too cumbersome, time consuming, and inaccurate In 1914 Krumbhaar,<sup>9</sup> summarizing the status of liver function tests, stated that no single test was yet satisfactory, but that the tetrachlor test of Rowntree looked the most promising In 1916 McNeil<sup>10</sup> improved the previous methods by inserting a duodenal tube into the duodenum before injection of the dye, and in 1921 Aaron, Beck, and Schneiders<sup>11</sup> modified the technic and introduced a stable preparation of the dye and estimated the phenoltetrachlorophthalein elimination in the bile In 1922 P F Williams<sup>12</sup> showed constant results in pathologic cases

Deakin and Graham<sup>13</sup> concluded that phenoltetrachlorophthalein is not a satisfactory substance to use in a liver functional test based on the quantitative estimation of its output in the bile They stated that there are too many factors to prevent a complete collection of bile through the duodenal tube

Working along similar lines, Piersol and Bockus<sup>14</sup> draw more favorable conclusions as to the value of the test

In 1922 Rosenthal did some original work and developed and improved the phenoltetrachlorophthalein test, in which he attempted to determine the amount of dye the liver would *not* excrete, in other words, how much was retained in the blood-plasma He injected 5 mg per kilo of body weight, after

having withdrawn 8 c.c. of blood for preparation of a colorimetric standard (1 c.c. of the dye solution equaled 50 mg. of the disodium salt), and found that this dosage was removed from the blood-stream very rapidly, in normal livers 2 to 60 per cent. was found present in the blood-plasma fifteen minutes after injection, and practically complete disappearance of the dye took place in forty to sixty minutes.

The technic of determining these percentages is to allow the blood withdrawn at the specified intervals to stand and cool for one hour, and centrifuge to remove the clear serum, and this tested for the dye remaining in it.

It is estimated that the blood-plasma contains 10 mg. of dye (as a result of the injection of 5 mg. per kilo body weight) per 100 c.c., and on this basis colorimetric standards are made. Three drops of 5 per cent. sodium hydroxid are added to the standards and the serum to be tested to bring out the color fully. Then, by simply matching the colors with the naked eye, a sufficient degree of accuracy as to the percentage in the blood-plasma is obtained. Readings are taken at certain specified intervals, namely, fifteen minutes, one hour, two hours, or even longer. A graft can be drawn to visualize the results.

In liver disease a high percentage of the dye is found in the blood-plasma for many hours. He concludes that the test gives an index of the total amount of functioning liver tissue and that clinical results have borne out experimental work. No dye was found in the urine in normal cases, whereas in cases of hepatic disease from traces to 4 to 6 per cent. were found in the urine, but the amount in the urine did not parallel the amount retained in the blood. No untoward effects were noted except that transitory induration of the vein wall at the sight of the injection was frequent, and in some cases localized thrombosis was present for several days.

Based on a large amount of clinical work, there is no foundation to believe that phenoltetrachlorophthalein in proper doses will damage the liver, and also it seems chemically impossible on a basis of the halogen content.

Some authors<sup>14</sup> have noticed dull pain in the region of the

liver after injections of the dye, also they have noticed the thrombosis and have suggested smaller injections to overcome this

It might be noted here that Ottenberg and Abramson<sup>15</sup> undertook some work to prove the upper safe limits of dosage of phenoltetrachlorophthalein and tetrabromphenolphthalein. Results were practically the same with the two dyes. Fifteen rabbits and 7 dogs were used. Doses of 0.1 gm (5 per cent. solution) per kilo body weight produced no symptoms or lesions except in one rabbit, and the substances injected did not appear in the urine. Doses of 0.2 gm per kilo produced some weakness and the substances were usually present in the urine. Lesions in the liver were minimal or absent. Doses from 0.3 to 0.4 gm per kilo made the animals very sick at once. Necropsies showed extensive degeneration of the liver lobules. Lesions were also present in the kidneys and spleens. Doses of from 0.4 to 0.5 gm per kilo killed the rabbits at once or within fifteen minutes, with acute convulsive symptoms.

It will be noted that doses needed to produce severe symptoms and liver lesions were enormously larger than those used in the phenoltetrachlorophthalein test for liver function.

Rosenfield and Schneider<sup>16</sup> believe strongly in the phenoltetrachlorophthalein test for function in pregnancy and the toxemias of pregnancy. They believe that the test will serve greatly as an index to treatment in the toxemias of pregnancy.

Some observations on the phenoltetrachlorophthalein test of liver function (duodenal tube method) are as follows<sup>17</sup>

Cases.	Initial time (minutes)	Maximum inten- sity (minutes)
1 (a) Syphiloma (intra-abdominal)	15	18
(b) After-treatment	13	18
2 Hepatic syphilis	43	43
3 Chronic nephritis	10	14
4 Chronic appendicitis (operated)	18	20
5 Chronic cholecystitis	19	23
6 Chronic cholangitis		26
7 Cholelithiasis (operated)	17	20
8 Chronic biliary infection (jaundice)		31
9 Hanot's cirrhosis	None in 2½ hours	
10 Sprue	12—	12
11 Pellagra	None in 1½ hours	
12 Chronic cholecystitis	18	30

Piersol and Bockus<sup>14</sup> did some work using the duodenal tube method, and in almost all cases their results were confirmed by the Rosenthal method

1. Cancer of stomach    Very slight retention
2. Cancer of esophagus    Very slight retention
3. Syphilis and arsphenamin therapy    Slight dysfunction, moderate in one case
4. Chronic cholecystitis    Very moderate retention
5. Diabetes    Slight disturbance of function
6. Arsphenamin jaundice    Marked retention
7. Hypertrophic cirrhosis    Marked retention
8. Metastatic carcinoma    Marked retention

These authors also give the report on 23 cases showing evidence clinically of liver disease. The test coincided in all except 2 cases.

In cases of complete obstruction of the duct with jaundice almost complete retention of the dye was found.

They experimented with rabbits and found that 12 per cent. of liver tissue had been removed before there was a deviation from the normal excretion.

Other authors have found most severe damage of function in cases of arsphenamin and catarrhal jaundice. Slight impairment in 90 per cent. of patients with secondary syphilis and cutaneous eruptions, moderate functional impairment was present in 7 cases of hepatic carcinoma, and moderate to mild impairment in 12 or 13 cases of cirrhosis.

Ottenberg, Rosenfeld, and Goldsmith<sup>15</sup> state that 5 per cent. of the dye in one-hour specimens is suspicious and 8 per cent. definitely indicates liver dysfunction.

**General Value in Diagnosis—*Interpretation of Test as Affected by Jaundice***—Every case that showed distinct jaundice from any cause, excepting pernicious anemia and hemolytic icterus, also showed some dye retention and usually about proportionate to the degree of jaundice.

***Positive Value of Test***—Most likely to be of diagnostic use in two conditions, namely, in confirmation of suspected liver cirrhosis and in detecting liver metastasis of malignant nature.

In cases where there is no obvious dysfunction of the liver clinically, but the diagnosis suggests such, is where the liver function tests are of importance and a distinct aid to diagnosis, as well as a guide to therapeutic management.

It is valuable also in diagnosing whether or not there has been any damage to the liver cells and, therefore, in a differential diagnosis between certain diseases, that is, in differentiating infections and catarrhal jaundice from yellow atrophy. When elimination is normal, even though jaundice continues, acute yellow atrophy can be ruled out. It is a most valuable aid in the toxemias of pregnancy, in drug poisoning it is of possible value, and it helps as a guide in treating syphilis by arsphenamin, as indicated by the constancy of dysfunction obtained in arsphenamin jaundice. It is particularly valuable in cases that appear to be normal, but really are found not to be, by the test.

*Negative Value of the Test*—It has only limited value because the liver has such an enormous reserve.

*Criteria for Ideal Dye*—Maurer and Gatewood<sup>19</sup> have set forth some conditions to be fulfilled for a dye to become ideal for a liver function test, namely, it must be non-toxic, it must be a crystalloid, its removal from the blood-stream must be solely by the liver, it must remain in the blood a sufficient length of time for a determination to be made, and its ultimate removal from the organism must be solely by the liver parenchyma cells. They did some work with phenoltetrachlorphthalein, and state, that of the five conditions, two are not fulfilled by phenoltetrachlorphthalein, that is, it is not a crystalloid and it is not removed from the blood-stream solely by the liver.

*Bromsulphthalein*—Rosenthal and White<sup>20</sup> have recently done some work with bromsulphthalein in testing for liver function. It is excreted in the bile of normal rabbits to the extent of 85 per cent in one hour after its intravenous injection. Normally, it is rapidly removed from the blood-stream through the activity of the liver cells, since, when the liver is extirpated it is retained in the blood-serum almost *in toto* during the early period following its injection. These are striking advantages over phenoltetrachlorphthalein, which when similarly injected

in rabbits is excreted in the bile to the extent of only 5 to 10 per cent. in one hour and which never reaches high concentration in the blood. The greater concentrations make it possible to use smaller doses, thus doing away with any irritating effect on the ven wall with thrombosis and possibly systemic reactions.

In normal animals, bromsulphthalein appears in the urine only in traces or not at all. Two mg of 5 per cent. solution per kilo are used. To establish normal values, tests were performed on 25 patients in whom no evidence of liver disease was present. Five minutes after injection an average of 35 per cent. of the dye was found in the serum. Thirty minutes after injection no dye remained, or so faint a trace as to be insufficient for colorimetric determination.

In 20 cases of liver disease studied with the bromsulphthalein test, retention of the dye in the blood thirty minutes after its injection varied from three to ninety-nine per cent.

Experimentally and clinically bromsulphthalein is more sensitive to liver impairment than phenoltetrachlorophthalein, but whether it will be of greater value in detecting early liver disease must await further clinical observation.

The authors state that the objection raised by Maurer and Gatewood are obviated by bromsulphthalein, as it is specifically handled by the liver, it circulates in the blood in a soluble form, and it is non-toxic in the dosage employed.

*Hemoclastic Crisis Test*—Widal's<sup>21</sup> hemoclastic crisis test merits some discussion here, it is based on proteopexic dysfunction. The introduction of proteose substances into the bloodstream so disturbs the colloidal balance of the blood as to produce a reaction of constant character, depending on the extent of liver damage, or inability of the liver to perform its normal physiologic action on the digested protein.

*Technic*—Leukocyte count, blood-pressure, pulse rate, coagulation of blood, and refraction index of blood are taken on a fasting stomach. The same procedure is repeated every twenty minutes after ingestion of 200 c.c. of milk. In cases of liver impairment there is a drop in the leukocyte count, blood-pressure, and pulse rate, hypercoagulability of blood, and decreased re-

fractive index of the blood-serum one or two hours after ingestion of the milk. The decrease in leukocyte count is very constant.

In normal persons the reaction is reversed, that is, there is a leukocytosis, an increased blood-pressure, pulse rate and hypercoagulation of blood, and increased refractive index

The leukocyte count is more constant and easiest to determine, therefore especial attention should be paid to it. There were 80 normal cases tried in this connection and not one failed to give a leukocytosis. However, it must be remembered, as Maurice points out, that the leukocytes fluctuate in a very wide range

-In comparing the hemoclastic crisis test with the phenol-tetrachlorophthalein test it was found that results were the same in a large number of cases with four exceptions, reasons for the exceptions not being apparent.<sup>6</sup> However, indications pointed to the hemoclastic crisis test as being the more delicate of the two tests in these cases according to the authors. Two of the cases were Banti's disease, 1 of amyloid degeneration of the liver, and 1 of chronic lead poisoning. There was a small retention of dye and a positive hemoclastic reaction in these cases

*Other Liver Function Tests*—Other tests for liver function to be considered more or less briefly are

Synthesis of urea from ingestion of ammonium salts, takes two or three times as long as usual

Tests with intramuscular injections of indigocarmin have obtained some favor, particularly by Hattiganis of Paris. Results with methylene-blue have been universally discouraging, and the test (excretion of methylene-blue in the bile after ingestion of 0.002 gm. by mouth) is considered practically useless

In attempts to determine liver function the feces and urine have been examined for the presence or absence of stercobilin, bilirubin, urobilin, and the biliary salts. Determinations have been made of the glycogenic and glycolytic functions, the proteolytic function, the proteopexic hemoclastic crisis test of Widal,<sup>21</sup> and various blood examinations

Hetenyi<sup>22</sup> determined bilirubin in blood and bile and considers 6 to 20 mg. per 100 c.c. as normal for bile, and up to 2.2 mg. in 199 c.c. as normal for blood

Filmski<sup>23</sup> believes that relative rise in the globulin content of the blood-serum may be a sign of insufficiency of the liver

Hecht and Noble<sup>24</sup> tested the liver function in children They concluded that the galactose test would not give reliable results, but the synthesis of camphor glycuronic acid was constant, with pathologic cases giving low values

Hess and Havemann<sup>25</sup> have used indigocarmin with comparatively good results, also Widal's hemoclastic test and the ingestion of sodium lactate

M Roch<sup>26</sup> devised a test dependent on the liver to transform sodium salicylate In insufficiency of the liver, a positive ferric chlorid test with urine consisting of a violet cloudy ring is obtained The salicylate causes the formation of glycuronic acid in the liver The findings were constant and reliable in 100 patients

Biscons and Rouzaud<sup>27</sup> stress the importance of blood examination for glucose, cholesterol, and urea. They say cholesteremia is to gall-stones what uricacidemia is to gout

It has been found that in drainage to the liver there is lessened coagulability of the blood and bleeding time is longer, consequently considerable efforts have been directed along this line Positive findings were accompanied by cholemia, urobilinuria, cholaluria, and the digestive leukopenia of Widal's hemoclastic crisis The abnormal bleeding time is a very early and sensitive test of liver derangement It returns to normal as soon as the liver functioning comes to normal again The Mayos<sup>28</sup> have reduced their mortality figures in cases of obstructive jaundice by a careful preoperative preparation of the patient to improve blood coagulability and bleeding time

van den Bergh<sup>29</sup> has applied Ehrlich's diazo reagent<sup>30</sup> as a chemical test for the detection and differentiation of minute amounts of either the free or the protein-fixed bilirubin in the blood-plasma The reagent must be freshly prepared

One c c of this mixture is added to 1 c c of plasma The instant appearance of a bluish-violet color, which is maximal in ten to thirty seconds is considered a direct or immediate reaction The occurrence of a direct reaction indicates free bili-



rubin on the blood-plasma, and consequently signifies obstructive jaundice. A delayed reaction (one in which a reddish color which gradually appears in from one to fifteen minutes) indicates impaired liver function.

An indirect reaction is one in which the direct test gives no color change, while, after 1 c c of blood-plasma is mixed with 2 c c of 96 per cent alcohol and the precipitate thrown down and 1 c c of the clear supernatant fluid treated with  $\frac{1}{4}$  c c of the reagent, gives an immediate violet-red color. The indirect reaction is due to the liberation by the alcohol of protein bound bilirubin. This signifies a hemolytic or functional jaundice.

**Summary**—1 The functions of the liver have been enumerated and this importance stressed both in normal and pathologic conditions.

2 Many functional tests for the liver have been devised, and a review of these shows them to have followed closely the known physiologic functions of the liver.

3 Tests based on the ability of the liver to excrete certain dyes are the most important to be considered, and of these Rosenthal's method seems to be predominant in importance, although there seems to be many points in favor of the other tests employed to determine liver function.

4 A brief history of liver function testing, dating back to the work of Abel and Rowntree in 1909 down to the present time, has been mentioned in connection, considering the various ways in which the phenoltetrachlorophthalein has been used, dwelling somewhat in detail upon the Rosenthal method.

5 Dysfunction has been found in practically all cases of liver disease, controls having been run. Cases cited in connection with results obtained.

6 The toxicity of phenoltetrachlorophthalein has seemed to be negligible in doses employed.

7 The employment of the phenoltetrachlorophthalein test in pregnancy and the toxemias of pregnancy has been shown to be of value.

8 In cases of arsphenamin jaundice and catarrhal jaundice marked liver dysfunction was always found. Results of a num-

ber of different investigators all coincides as regards these two conditions particularly

9 The phenoltetrachlorphthalein test is shown to be practical in cases of obstructive jaundice in telling when obstruction is relieved because of prolonged return of liver function

10 General value in diagnosis in regard to value in cases associated with jaundice, positive value, and negative value is discussed

11 Five conditions must be fulfilled for a dye to become ideal in testing for liver function. Objection has been raised to phenoltetrachlorphthalein. Bromsulphthalein has been suggested as a dye to overcome these objections, and on the whole this dye seems to be more promising than phenoltetrachlorphthalein.

12 Widal's hemoclastic crisis test, based on proteopexic dysfunction is discussed. A comparison of it with the phenoltetrachlorphthalein test gives favorable results. Indications point to it being a sensitive test for detecting liver impairment.

13 van den Bergh's test is shown to be of value. A direct reaction indicates obstructive jaundice. A delayed reaction indicates impaired liver function. An indirect reaction signifies a hemolytic jaundice.

**Conclusion** —Following the development of the various methods for determining the functional capacity of the liver, there has been remarkable advancement made in diagnosing obscure conditions of the liver, in following the course of a disease, estimating the amount of liver damage, and in telling what benefit has been derived from treatment.

The liver is the largest single organ in the body, and it is essential for health and a continuation of life, as has been said. It is only of late years that some light has dawned on its important functions. It is for these reasons that functional tests of the liver have aroused so much interest, and endeavors have been rewarded by valuable discoveries. However, by no means should the impression be left that the last word has been said in regard to liver function and liver function testing, because we may expect new methods in testing the functional capacity of the liver as new discoveries are made concerning its physiology.

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# CLINIC OF DR ROBERT E BRATTON

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### ETIOLOGY AND TREATMENT OF SCARLET FEVER

It is my purpose to attempt to summarize for you the work that has been carried out in attempting to arrive at a definite etiology and specific treatment of the disease scarlet fever. In going over the literature I find that a vast amount of work in the past few years has been done on this disease along the lines of etiology and treatment. Some have worked with the idea that it is caused by a filtrable virus and some that it was protozoal in origin. However, most of the investigators seem to have had the idea that some strain of streptococcus was responsible for the disease and have attempted to treat the disease with an antistreptococcal serum.

**Historical**—As early as 1895 Marmorek<sup>1</sup> recognized the frequency with which the *Streptococcus hemolyticus* was present in the throat secretions from scarlet fever patients and inclined toward the belief that this organism might be the possible etiologic factor in the production of the disease. Consequently he prepared an antistreptococcal serum against scarlet fever, immunizing animals with polyvalent strains of *Streptococcus hemolyticus* from the throat secretions of scarlet fever patients in the acute stages of the disease. Unfortunately clinical trials with the serum boded ill for its success and it was soon forgotten.

Again in 1897 we have the works of Weisbecker<sup>2</sup>. He assumed that persons who had recently passed through an attack of scarlet fever would have specific antibodies in their blood, and if these antibodies were in sufficient concentration, the serum of such blood might be of a curative value when introduced into patients acutely ill with the disease, as a result of this, he treated

5 cases of scarlet fever with blood-serum from convalescents, but his results were also disappointing

From 1899 to 1903 scarlet fever cases were treated by the injection of cow-serum by H. Ber, von Leyden, Rupel, and Schaez. But they failed to accomplish what they had hoped for and, due to the failure of these workers to obtain results, this form of treatment was dropped for the time being.

In 1903 we see an article by Hektoen,<sup>3</sup> who correlated the results of such works as Pierce, Wright, Lemanne, Bobes, and Roskin, all of whom cultured the blood from scarlet fever patients and found the streptococcus to be present in a number of cases.

Klein was one of the first at that time to describe cocci as the cause of scarlet fever. He found the organism in the blood of 4 cases out of 9 scarlet fever patients.

As a result of the positive findings at this time, work was begun on a serum for this condition. Note is made here of Merey, who found the streptococcus which he isolated from the blood of scarlet fever patients was refractory to an antistreptococcal serum that was made by Marmorek.

After summing up the results of the experiments carried out at this period Hektoen concluded that he was not sure whether the streptococcus was the cause or merely the result of secondary infection in scarlet fever, as it seemed to be found more frequently in the more severe and protracted cases of scarlet fever in which also developed the clinical signs of a general infection, such as joint inflammations, and streptococci were not found in many of the fatal cases of scarlet fever.

In 1905 we have the works of Gabrickensky,<sup>4</sup> a Russian physician, who prepared a streptococcal vaccine to be used as a prophylactic treatment in scarlet fever. He was probably the first to advocate the practice of streptococcal immunization in scarlet fever. He prepared a vaccine from cultures of streptococci secured at autopsy of scarlet fever patients, and he reports some very good results from his works.

Kolmer<sup>4</sup> in 1912 attempted to prove the results obtained by Gabrickensky. He immunized 350 patients, following the tech-

nic employed by the Russian, but failed to get good results reported by the Russian, and he stated the reports of Gabrickensky concerning the efficiency of injection of streptococcal vaccine as a preventive of scarlet fever was, on the whole, quite convincing in spite of the fact that he himself had failed to corroborate the findings. He also stated that he believes a streptococcal immunization might not only prevent scarlet fever, but would probably prevent secondary streptococcal infection.

Weaver, in his article in 1918, also mentioned some results of work done in 1912 by Reiss and Jangmono, who treated 12 cases of scarlet fever by intravenous injections of 40 to 100 c c of convalescent serum, with marked benefit in all cases. They drew the blood from convalescent patients about the third week and mixed the serum from several cases. The next year Hack reported from the same clinic the treatment for 22 additional patients with one death. He noted a prompt fall in the temperature and a marked rapid general improvement of patients from this method when treated early in the disease. He emphasized the early treatment.

Also, in 1918 Reiss and Hertz reported still larger series of cases in which the results were most satisfactory. In the fall of this same year we have the reports from Zinger,<sup>5</sup> who treated 15 cases of very severe cases of scarlet fever with four deaths, using fresh blood from convalescent scarlet fever cases. Two of these died from septic conditions, and the other 2 who died were moribund when they were injected. Five cases were of the purely toxic type, and the other 6 patients had additional septic complications. The 5 purely toxic cases showed a critical drop in temperature, after which it remained normal or slightly above normal. In the 6 remaining cases the drop in temperature was less marked and was followed by a secondary rise which persisted for a number of days. His treatment was to inject 75 to 200 c c intramuscularly into these cases.

Weaver in 1918 carried out his work along the lines of Reiss, Jugman, and Zinger. He treated 10 cases of scarlet fever by injecting 25 to 90 c c of convalescent serum intramuscularly. All of his patients recovered, although he selected the sickest,

and some of them seemed about hopeless. The result he noted was a fall in temperature, beginning two to four hours after the serum was injected, and continued, its height being reached in twelve to twenty-four hours. In the purely toxic cases the temperature fell nearly to normal and observed little tendency to rise again, but in the cases with septic complications the initial fall occurred, but there was a secondary rise. However, there was a general improvement and the fever did not rise again to its original height, and, on the whole, the disease appeared to be favorably altered by this serum. During twelve to twenty-four hours of the injection of the serum, more striking than the fall of the temperature, was the improvement in the general condition of the patient. This was most pronounced in the purely toxic cases and also very poor in the septic ones. Delirium subsided, the pulse became slower and improved in quality, and cyanosis disappeared. In 2 cases a fall of temperature and a general improvement followed the injection of serum, but fever rose again and the general condition became worse. A second injection of serum was followed by a rapid improvement.

He was of the belief that the patients who received serum early were most greatly influenced, as his last results were obtained in cases in the fourth and fifth days of the disease, and he believes that if the serum were given early in all cases some of the later septic complications could be avoided.

His conclusions were that, although scarlet fever usually runs a relatively short course and frequently terminated by crisis, too much credit must not be given to the serum in all cases. However, he states that the happy course taken by so many cases of severe scarlet fever as have been reported when treated with the serum could hardly be due to a coincidence.

**Schultz-Charlton Reaction** —From the reports of Toony and Nourse,<sup>6</sup> we have the results of the works of Schultz and Charlton, who in 1918 first observed that intracutaneous injections of 0.5 to 1 c c of serum from normal persons or persons convalescent from scarlet fever caused a definite blanching of the rash in patients with scarlet fever. The blanching phenomena occurred

within five or six hours following the injection and the area blanched measured 2.5 to 5 cm in diameter. They found in a series of 50 typical cases of scarlet fever that positive blanching was obtained in 44 of them, or 88 per cent, that doubtful reactions occurred in 5, or 10 per cent, and there was no blanching in 1 or 2 per cent. The areas blanched were found to persist until the general exanthema had faded. A few years later Neuman confirmed these observations, and noted that serum withdrawn from patients during the first four days of an attack of scarlet fever did not produce the blanching phenomena. Hainiss found, in a series of 19 cases tested with convalescent serum, that positive blanching reactions were obtained in 11, or 58 per cent. At this time Paschen reported the results of a series of 71 cases tested with convalescent serum, in which positive blanching reactions were obtained in 61, or 87 per cent.

The following year Schultz examined his earlier work and likewise confirmed the findings of Neuman. He had observed positive blanching reactions with convalescent serum in 100 per cent of scarlet fever patients tested on the second day of the disease, in 78 per cent tested on the third day of the disease, and in 70 per cent of 5 cases each tested on the first and fourth days of the disease. Cases tested on the fifth day of the disease gave uniformly negative reactions. At this time Tron reported the results of 50 cases of scarlet fever tested with convalescent serum in various stages of the disease and observed the blanching phenomena in only 10, or 21 per cent.

A number of other men at that time tried out the tests with various results similar to those listed above. In reviewing the literature concerning the Schultz-Charlton phenomena one finds a difference of opinion as regards the value of this test. On the one hand, Neuman is inclined to regard it as a specific diagnostic phenomena, while on the other hand, Tron and others considered it worthless in the doubtful cases of scarlet fever.

Toony and Nourse, following the ideas of these men, carried out a series of experiments. They tested 14 cases of definite scarlet fever at the height of the rash, using the following solution: epinephrin 1:1000, the stock typhoid triple vaccine,



physiologic salt solution, horse-serum, and serum from convalescent scarlet fever patients of about three weeks' duration, 1 c c doses being used. They found here that epinephrin produced blanching in all cases. The reactions, however, differing from that produced with human serum in that it began in a few moments and disappeared in from five to six hours, the blanched area was much paler than normal skin, and was surrounded by a definite red margin from 3 to 6 cm wide. The blanching obtained with the human serum appeared in from six to eight hours and persisted until the rash faded. The foreign protein in the form of stock typhoid vaccine and horse-serum produced no typical blanching, although there were three instances of horse-serum injections in which rather indefinite disappearance of the rash occurred.

When an additional 8 cases were tested with convalescent scarlet fever serum 7 positive reactions out of 8 were obtained.

Normal serum was then compared with serum from convalescent scarlet fever patients in the fourth week of the disease, and gave a higher percentage of positive reactions.

Serum from definite scarlet fever cases during the first week of the disease was injected in 18 cases, normal human serum being employed for a control, with a result of eighteen positive reactions with the normal human serum and eighteen negative reactions with the antiscarlatinal serum, using 1 c c doses.

After carrying a considerable amount of work along this line these 2 men concluded that there is present in the blood of some normal and some cases of scarlet fever serum a substance which, when injected intradermally, will cause the rash of scarlet fever to disappear at the site of injection, as was first pointed out by Schultze and Charlton.

**Present-day Studies** —In 1919 Dochez,<sup>7</sup> Avery, and Lansfield developed a technic of differentiation of biologic types of *Streptococcus hemolyticus*. This test led to the re-examination of the type of streptococcus associated with scarlet fever and they attempted to produce scarlet fever in animals. They succeeded in producing a condition in guinea-pigs that resembled scarlet fever. The animals developed fever, leukocytosis, loss of weight,

and on the second and third days showed a transient hyperemic flush, and on the eighth to the twelfth days more or less general desquamation, most conspicuously on the pads of the feet

In view of the similarity to scarlet fever of this symptom-complex produced in guinea-pigs they immunized a horse, and produced the Dochez antistreptococcal serum that was tested out later by Frances Blake

Blake<sup>8</sup> worked with Lynch in testing out the Dochez serum. They started out with two ideas in view, first, to prove that the local blanching described by Schultz and Charlton could be demonstrated with Dochez serum. They used 0.5 to 1 c.c. of this serum in a series of cases and got practically the same results as had been described by Schultz and Charlton. They then set out to endeavor to prove the therapeutic value of Dochez' serum using large doses.

They treated 1907 cases of scarlet fever in New Haven from January 1 to July 1, 1924, and there were only two deaths, and one of these cases occurred in Blake's series of 13 cases.

They found that when the serum was given early in the disease there was a definite fading of the rash apparent within twenty-four hours, and that there was an improvement in the toxic symptoms, so that the antitoxin was said to remove the toxic element of the disease, including the rash.

Their series of cases were too small to definitely establish the value of this serum, but they concluded from this small series of cases Dochez's antiscarlatinal serum had shown that it was a valuable therapeutic agent in the treatment of scarlet fever.

In 1923 and 1924 we have the results of Langer's<sup>9</sup> experiments who worked in a scarlet fever epidemic in Brum.

He used a serum from scarlet fever patients, and administered this serum in amounts varying from 30 to 70 c.c. according to the age of the patient and the severity of the disease. Forty cases were treated with this serum, at least 5 of these were severe toxic cases of scarlet fever. The injection of this serum was made in different stages of the disease. In all the cases beneficial effects were evident in a short time. Besides the favorable effects on the temperature the serum exerted a favor-

able effect on the general symptoms. Delirious children a few hours after the injection went into a deep sleep from which most of them arose greatly refreshed. Likewise the effects on the circulation of the blood, the decrease of the pulse frequency, and disappearance of cyanosis of the exanthem were clearly observed. The development, intensity, and duration of the exanthem was uninfluenced by the serum treatment, this is in accord with the results reported by Bode.

Langer as well as Bode found that often injection of more than half of all cases after the critical defervescence proceeded fever free throughout the period of convalescence, and any complication took a very light course.

In explaining the action of the serum he suggested that it was due to a specific effect of the serum, furthermore, he believed that its use is indicated in severe toxic scarlet fever.

Lastly we come to the latest work upon the subject of scarlet fever which has been carried out by the Dicks.<sup>10</sup>

Up until the recent works of the Dicks scarlet fever had not been successfully produced artificially. Many attempts had been made along this line which, if results had been satisfactory, would have settled the etiology of scarlet fever, however, we see that a real production of experimental scarlet fever remained the essential step in determining the etiology of the disease.

In order to learn if it were possible to obtain an acceptable scarlet fever in laboratory animals, they were inoculated in the throat subcutaneously, intraperitoneally, and intravenously with fresh blood-serum, blood-plasma, whole blood, throat mucous, and urinary sediment from early cases of scarlet fever, and macerated skin scales from desquamating cases. They were inoculated with ground tonsils, lymph-glands, and spleens obtained as soon as possible after death. It was reasonable to believe that in some of the inoculations each species of animal used had received material containing the specific organism of scarlet fever. The negative results of these experiments led them to conclude that laboratory animals are comparatively insusceptible, and that it would be necessary to use human volunteers for the production of experimental scarlet fever.

Before attempting the human experiments they attempted to determine by means of immune reactions where in the body of scarlet fever patients the specific organism existed in the greatest abundance. The results of their bacteriologic examinations and immune reactions indicated that the specific organism of scarlet fever was present in throat mucus, but was not present in the blood, of the early uncomplicated cases as was thought by some.

After finding that the organism was in the throat, the next step was to find out if it was a filtrable virus. They selected volunteers of an intelligent type who could give a full personal and family history and had spent their childhood in rural districts or in homes where an ordinary attack of scarlet fever would probably have been recognized.

In this series they obtained a case of typical scarlet fever by inoculating with a pure culture of hemolytic streptococcus isolated from a lesion on the finger of a nurse who acquired the disease while caring for a convalescent scarlet fever patient. This was the first case of scarlet fever produced experimentally by the inoculation of a pure culture of any organism. It was reported October 6, 1924.

Since the greatest difficulty in determination of the etiology of scarlet fever has now been overcome, they next attempted to prove whether or not it was caused by a filtrable virus.

A second group of volunteers were inoculated with a culture of the same organism after it had been passed through a Berkefeld filter. These volunteers remained well. After two weeks had elapsed, and they were still well, they were inoculated with unfiltered cultures. Forty-eight hours later one of them developed scarlet fever, which furnished further evidence to prove that scarlet fever was not produced by a filtrable virus, but by the hemolytic streptococcus itself.

At this time they also proved the value of the culture of the organism in determining the susceptibility of the individual to scarlet fever. They did this by carrying out the skin tests on volunteers until they obtained a negative and a positive one. They took these two and were able to produce experimental

scarlet fever in the one with the positive skin test, and were unable to produce it in the one with the negative skin test

The hemolytic streptococcus used in their experiments had now fulfilled all the requirements of Koch's laws, and the conclusion that it is the cause of scarlet fever was justified

The proof that the positive skin reactions in persons who had not had scarlet fever were not due to foreign protein in the culture was shown by negative results on intradermal injections of undiluted sterile culture-media

Further evidence of the specific relation of this test to scarlet fever was offered by the following experiment

A mixture of equal volumes of the filtrate with convalescent scarlet fever sera were inoculated, 2 c c being used Control mixtures of salt solution and filtrate were also inoculated Skin tests were made with the two mixtures in persons who had previously shown positive reactions At the end of twenty-four hours the tests with sera mixtures were negative, while those in which salt solution had been used mixed with the filtrate were positive

These results indicated that the blood of convalescent scarlet fever patients contains a substance capable of inhibiting the action of the filtrate on the skin

Persons with positive skin tests were then given convalescent scarlet fever serum by intramuscular injections Skin tests made after this passive immunization were negative

As a result of their observations the Dicks have produced an antistreptococcal serum for treatment of scarlet fever patients

**Technic of Dick's Test**—This test is similar to that of Schick, 1/10 c c of the diluted toxin is injected intradermally on the right forearm for the test, and a similar amount of the heated toxin on the left forearm for the control

There are four different reactions that can be distinguished with the test and the control test There is a positive, a negative, a pseudoreaction, and a positive combined reaction These reactions very closely resemble the reactions noted with the Schick test

To make the reading of the Dick reaction more accurate and to avoid the confusion that is very likely to arise in the interpretation between the positive and pseudoreactions Dick strongly recommends a control test with toxin that has been heated in a preliminary dilution of 1 100 and in a final dilution of 1 1000 in a water bottle at a boiling temperature for one hour This heated toxin, as stated above, is injected into the left forearm as a control

If the skin tests are positive, active immunization with scarlet fever toxin is advised The amount is most conveniently increased by the skin test dose, the quantity injected representing 100 and 250 skin doses for children under twelve years, and 100, 250, and 500 skin test doses for persons over twelve years of age The injections are given one week apart The immunity results as shown by the Dick test seem to be encouraging A large proportion of the selected individuals show a pseudoreaction, indicating the necessity of adding the control test to the Dick test in checking upon the immunity results with scarlet fever toxin

As a therapeutic agent the serum is used in doses ranging from about 40 to 100 c c intramuscularly Dr Jones, of Charity Hospital has used it in this manner and has failed to get the results claimed by the Dicks However, this may be due to the fact that the true Dick serum is not on the market as yet, and Dr Jones used the serum that is put out by one of the drug houses and which is supposed to be one of the same strain of streptococci as the true Dicks' serum

Summary —Often reviewing the literature upon the subject it seems to me that the Dicks have probably completed the work which was begun by Mormorek in 1895 They have isolated an organism from an undoubted case of scarlet fever, having inoculated the organism into human volunteer subjects, reproducing in them all the signs and symptoms of scarlet fever, and have recovered the organism again This fulfils all the exacting postulates of Koch They have recovered from filtrates of the organism a poison the principle of which, when injected into men, induces a quantitative and qualitative reaction indicative of the

susceptibility of scarlet fever They have produced immunity or a very decided degree of tolerance to infection with the scarlet fever microbe with properly graduated injections of this poison

Conclusion.—If this recent work of the Dicks can be corroborated by competent investigators it appears to me that we now have the long-hoped-for, specific treatment for the disease scarlet fever

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